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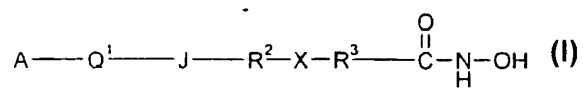
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(54) Title: CARBAMIC ACID COMPOUNDS COMPRISING AN ETHER LINKAGE AS HDAC INHIBITORS



(I)

(57) Abstract: This invention pertains to certain active carbamic acid compounds which inhibit HDAC activity and which have the following formula(I) wherein: A is an aryl group; Q^1 is a covalent bond or an aryl leader group; J is an amide linkage selected from: $-NR^1C(=O)-$ and $-C(=O)NR^1-$; R_1 is an amido substituent; X is an ether heteroatom, and is -O- or -S-; and, R^2 and R^3 are each independently an ether group; and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both in vitro and in vivo, to inhibit HDAC, and, e.g., to inhibit proliferative conditions, such as cancer and psoriasis.

CARBAMIC ACID COMPOUNDS COMPRISING AN ETHER LINKAGE AS HDAC INHIBITORS

RELATED APPLICATION

This application claims priority to United Kingdom Patent Application Number GB 0023983.0 filed 29 September 2000, the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

This invention pertains generally to the field of biologically active compounds, and more specifically to certain active carbamic acid compounds which inhibit HDAC (histone deacetylase) activity. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit HDAC, and, e.g., to inhibit proliferative conditions, such as cancer and psoriasis.

BACKGROUND

DNA in eukaryotic cells is tightly complexed with proteins (histones) to form chromatin. Histones are small, positively charged proteins which are rich in basic amino acids (positively charged at physiological pH), which contact the phosphate groups (negatively charged at physiological pH) of DNA. There are five main classes of histones, H1, H2A, H2B, H3, and H4. The amino acid sequences of histones H2A, H2B, H3, and H4 show remarkable conservation between species, whereas H1 varies somewhat, and in some cases is replaced by another histone, e.g., H5. Four pairs of each of H2A, H2B, H3, and H4 together form a disk-shaped octomeric protein core, around which DNA (about 140 base pairs) is wound to form a nucleosome. Individual nucleosomes are connected by short stretches of linker DNA associated with another histone molecule (e.g., H1, or in certain cases, H5) to form a structure resembling a beaded string, which is itself arranged in a helical stack, known as a solenoid.

The majority of histones are synthesised during the S phase of the cell cycle, and newly synthesised histones quickly enter the nucleus to become associated with DNA. Within minutes of its synthesis, new DNA becomes associated with histones in nucleosomal structures.

A small fraction of histones, more specifically, the amino side chains thereof, are enzymatically modified by post-translational addition of methyl, acetyl, or phosphate groups, neutralising the positive charge of the side chain, or converting it to a negative charge. For example, lysine and arginine groups may be methylated, lysine groups may be acetylated, and serine groups may be phosphorylated. For lysine, the $-(CH_2)_4-NH_2$ sidechain may be acetylated, for example by an acetyltransferase enzyme, to give the amide $-(CH_2)_4-NHC(=O)CH_3$. Methylation, acetylation, and phosphorylation of amino termini of histones which extend from the nucleosomal core affects chromatin structure and gene expression. (See, for example, Spencer and Davie, 1999).

Acetylation and deacetylation of histones is associated with transcriptional events leading to cell proliferation and/or differentiation. Regulation of the function of transcription factors is also mediated through acetylation. Recent reviews of histone deacetylation include Kouzarides, 1999 and Pazin et al., 1997.

The correlation between the acetylation status of histones and the transcription of genes has been known for over 30 years (see, for example, Howe et al., 1999). Certain enzymes, specifically acetylases (e.g., histone acetyltransferase, HAT) and deacetylases (e.g., histone deacetylase, HDAC), which regulate the acetylation state of histones have been identified in many organisms and have been implicated in the regulation of numerous genes, confirming the link between acetylation and transcription. See, for example, Davie, 1998. In general, histone acetylation correlates with transcriptional activation, whereas histone deacetylation is associated with gene repression.

A growing number of histone deacetylases (HDACs) have been identified (see, for example, Ng and Bird, 2000). The first deacetylase, HDAC1, was identified in 1996 (see, for example, Tauton et al., 1996). Subsequently, two other nuclear mammalian deacetylases has been found, HDAC2 and HDAC3 (see, for example, Yang et al., 1996, 1997, and Emiliani et al., 1998). See also, Grozinger et al., 1999; Kao et al., 2000; and Van den Wyngaert et al., 2000.

Eight human HDACs have been cloned so far:

HDAC1 (Genbank Accession No. NP_004955)
HDAC2 (Genbank Accession No. NP_001518)
HDAC3 (Genbank Accession No. O15739)
HDAC4 (Genbank Accession No. AAD29046)
HDAC5 (Genbank Accession No. NP_005465)
HDAC6 (Genbank Accession No. NP_006035)
HDAC7 (Genbank Accession No. AAF63491)
HDAC8 (Genbank Accession No. AAF73428)

These eight human HDACs fall in two distinct classes: HDACs 1,2,3 and 8 are in class I, and HDACs 4,5,6 and 7 are in class II.

There are a number of histone deacetylases in yeast, including the following:

RPD3 (Genbank Accession No. NP_014069)
HDA1 (Genbank Accession No. P53973)
HOS1 (Genbank Accession No. Q12214)
HOS2 (Genbank Accession No. P53096)
HOS3 (Genbank Accession No. Q02959)

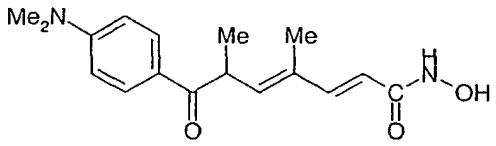
There are also numerous plant deacetylases, for example, HD2, in Zea mays (Genbank Accession No. AF254073_1).

HDACs function as part of large multiprotein complexes, which are tethered to the promoter and repress transcription. Well characterised transcriptional repressors such as Mad (Laherty et al., 1997), pRb (Brehm et al., 1998), nuclear receptors

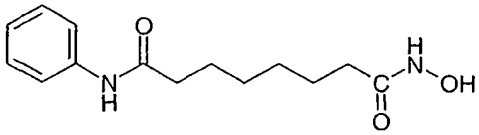
(Wong et al., 1998) and YY1 (Yang et al., 1997) associate with HDAC complexes to exert their repressor function.

The study of inhibitors of histone deacetylases indicates that these enzymes play an important role in cell proliferation and differentiation. The inhibitor Trichostatin A (TSA) (Yoshida et al., 1990a) causes cell cycle arrest at both G1 and G2 phases (Yoshida and Beppu, 1988), reverts the transformed phenotype of different cell lines, and induces differentiation of Friend leukaemia cells and others (Yoshida et al., 1990b). TSA (and SAHA) have been reported to inhibit cell growth, induce terminal differentiation, and prevent the formation of tumours in mice (Finnin et al., 1999).

Trichostatin A (TSA)



Suberoylanilide Hydroxamic Acid (SAHA)



Cell cycle arrest by TSA correlates with an increased expression of gelsolin (Hoshikawa et al., 1994), an actin regulatory protein that is down regulated in malignant breast cancer (Mielnicki et al., 1999). Similar effects on cell cycle and differentiation have been observed with a number of deacetylase inhibitors (Kim et al., 1999).

Trichostatin A has also been reported to be useful in the treatment of fibrosis, e.g., liver fibrosis and liver cirrhosis. See, e.g., Geerts et al., 1998.

Recently, certain compounds that induce differentiation have been reported to inhibit histone deacetylases. Several experimental antitumour compounds, such

as trichostatin A (TSA), trapoxin, suberoylanilide hydroxamic acid (SAHA), and phenylbutyrate have been reported to act, at least in part, by inhibiting histone deacetylase (see, e.g., Yoshida et al., 1990; Richon et al., 1998; Kijima et al., 1993). Additionally, diallyl sulfide and related molecules (see, e.g., Lea et al., 1999), oxamflatin (see, e.g., Kim et al., 1999), MS-27-275, a synthetic benzamide derivative (see, e.g., Saito et al., 1999; Suzuki et al., 1999; note that MS-27-275 was later re-named as MS-275), butyrate derivatives (see, e.g., Lea and Tulsyan, 1995), FR901228 (see, e.g., Nokajima et al., 1998), depudecin (see, e.g., Kwon et al., 1998), and m-carboxycinnamic acid bishydroxamide (see, e.g., Richon et al., 1998) have been reported to inhibit histone deacetylases. *In vitro*, some of these compounds are reported to inhibit the growth of fibroblast cells by causing cell cycle arrest in the G1 and G2 phases, and can lead to the terminal differentiation and loss of transforming potential of a variety of transformed cell lines (see, e.g., Richon et al, 1996; Kim et al., 1999; Yoshida et al., 1995; Yoshida & Beppu, 1988). *In vivo*, phenybutyrate is reported to be effective in the treatment of acute promyelocytic leukemia in conjunction with retinoic acid (see, e.g., Warrell et al., 1998). SAHA is reported to be effective in preventing the formation of mammary tumours in rats, and lung tumours in mice (see, e.g., Desai et al., 1999).

The clear involvement of HDACs in the control of cell proliferation and differentiation suggests that aberrant HDAC activity may play a role in cancer. The most direct demonstration that deacetylases contribute to cancer development comes from the analysis of different acute promyelocytic leukaemias (APL). In most APL patients, a translocation of chromosomes 15 and 17 (t(15;17)) results in the expression of a fusion protein containing the N-terminal portion of PML gene product linked to most of RARα (retinoic acid receptor). In some cases, a different translocation (t(11;17)) causes the fusion between the zinc finger protein PLZF and RARα. In the absence of ligand, the wild type RARα represses target genes by tethering HDAC repressor complexes to the promoter DNA. During normal hematopoiesis, retinoic acid (RA) binds RARα and displaces the repressor complex, allowing expression of genes implicated in myeloid differentiation. The RARα fusion proteins occurring in APL patients are no longer responsive to physiological levels of RA and they interfere with the expression of

the RA-inducible genes that promote myeloid differentiation. This results in a clonal expansion of promyelocytic cells and development of leukaemia. *In vitro* experiments have shown that TSA is capable of restoring RA-responsiveness to the fusion RARα proteins and of allowing myeloid differentiation. These results establish a link between HDACs and oncogenesis and suggest that HDACs are potential targets for pharmaceutical intervention in APL patients. (See, for example, Kitamura et al., 2000; David et al., 1998; Lin et al., 1998).

Furthermore, different lines of evidence suggest that HDACs may be important therapeutic targets in other types of cancer. Cell lines derived from many different cancers (prostate, colorectal, breast, neuronal, hepatic) are induced to differentiate by HDAC inhibitors (Yoshida and Horinouchi, 1999). A number of HDAC inhibitors have been studied in animal models of cancer. They reduce tumour growth and prolong the lifespan of mice bearing different types of transplanted tumours, including melanoma, leukaemia, colon, lung and gastric carcinomas, etc. (Ueda et al., 1994; Kim et al., 1999).

Psoriasis is a common chronic disfiguring skin disease which is characterised by well-demarcated, red, hardened scaly plaques: these may be limited or widespread. The prevalence rate of psoriasis is approximately 2%, i.e., 12.5 million sufferers in the triad countries (US/Europe/Japan). While the disease is rarely fatal, it clearly has serious detrimental effects upon the quality of life of the patient: this is further compounded by the lack of effective therapies. Present treatments are either ineffective, cosmetically unacceptable, or possess undesired side effects. There is therefore a large unmet clinical need for effective and safe drugs for this condition.

Psoriasis is a disease of complex etiology. Whilst there is clearly a genetic component, with a number of gene loci being involved, there are also undefined environmental triggers. Whatever the ultimate cause of psoriasis, at the cellular level, it is characterised by local T-cell mediated inflammation, by keratinocyte hyperproliferation, and by localised angiogenesis. These are all processes in which histone deacetylases have been implicated (see, e.g., Saunders et al.,

1999; Bernhard et al, 1999; Takahashi et al, 1996; Kim et al , 2001). Therefore HDAC inhibitors may be of use in therapy for psoriasis. Candidate drugs may be screened, for example, using proliferation assays with T-cells and/or keratinocytes.

Thus, one aim of the present invention is the provision of compounds which are potent inhibitors of histone deacetylases (HDACs). There is a pressing need for such compounds, particularly for use as antiproliferatives, for example, anti-cancer agents, agents for the treatment of psoriasis, etc.

Such molecules desirably have one or more of the following properties and/or effects:

(a) easily gain access to and act upon tumour cells;
(b) down-regulate HDAC activity;
(c) inhibit the formation of HDAC complexes;
(d) inhibit the interactions of HDAC complexes;
(e) inhibit tumour cell proliferation;
(e) promote tumour cell apoptosis;
(f) inhibit tumour growth; and,
(g) complement the activity of traditional chemotherapeutic agents.

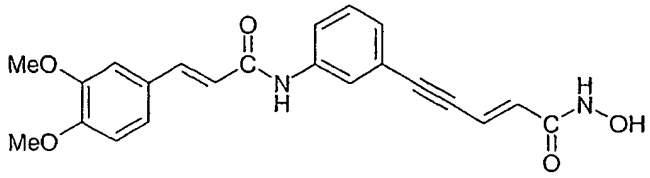
A number of carbamic acid compounds have been described.

Amides

Hashimoto et al., 1989 describe hydroxamic acid compounds which are claimed to inhibit cell proliferation. Some of the compounds are carbamic acid compounds having a substituted phenyl-dione group linked to a carbamic acid group (-CONHOH) via an aryl-substituted alkylene group.

Ohtani et al., 1993 describe a number of hydroxamic acid compounds which are claimed to be inhibitors of ras transformation. A few of the compounds are carbamic acid compounds having a phenylacylamido group (-NHCOPh) linked to

a carbamic acid group (-CONHOH) via a phenylene-meta-alkylene group having a carbon-carbon triple bond. See, for example, compounds I-29 (page 69), I-39 (page 87), and I-41 (page 90). Compound I-41, shown below, employs an aryl leader.



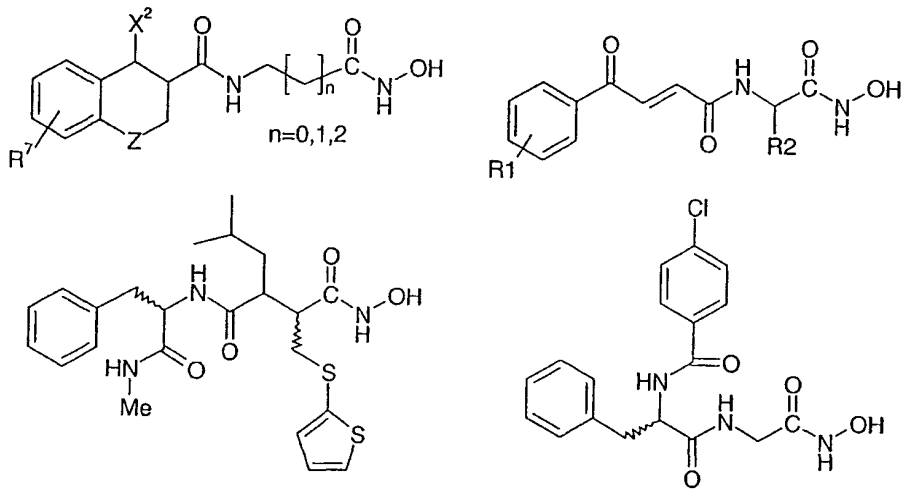
Onishi et al., 1996, describe several hydroxamic acid compounds which have a phenyl (or substituted phenyl) group linked via an oxazole group to a carbamic acid group. These compounds were reported to inhibit a deacetylase enzyme critical in the biosynthesis of lipid A (a component of the outer membrance of Gram-negative bacteria).

Parsons et al., 1998 describe a number of hydroxamic acid compounds which are claimed to selectively prevent the growth of a variety of human tumour cell lines.

Some of the compounds are carbamic acid compounds having an arylamide group linked to a carbamic acid group via a methylene or substituted methylene group (see, for example, pages 16 and 17).

Some of the compounds are carbamic acid compounds having a phenylamido group (-CONHPh) linked to a carbamic acid group (-CONHOH) via a long alkylene chain, $-(CH_2)_n-$, wherein n is from 4 to 7 (see, for example, pages 47, 48, and 58 therein).

Some of the compounds are carbamic acid compounds having an aryl group linked via a short chain to an amide group (-CONH-), which in turn is linked via a short chain (e.g., 3 atoms or less) to a carbamic acid group (-CONHOH) (see, for example, page 16, 2nd formula; page 46, 4th formula; page 51, compound 7; and page 61, 2nd formula, therein).



Richon et al., 1998 describe several hydroxamic acid compounds, including SAHA, which apparently inhibit HDAC activity, and induce terminal differentiation and/or apoptosis in various transformed cells (see, for example, Table 1 therein).

Suzuki et al., 1998 describe a number of hydroxamic acid compounds which are claimed to have antitumour activity. Some of the compounds are carbamic acid compounds having a substituted phenylamido group (-CONHPh) linked to a carbamic acid (-CONHOH) group via a phenylene-meta-ethenylene or phenylene-para-ethylene group (see, for example, pages 8 and 9, compounds 31-50).

Breslow et al., 1994, 1995, 1997 describe a number of hydroxamic acid compounds which are claimed to selectively induce terminal differentiation of neoplastic cells.

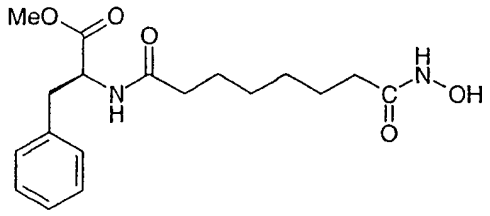
Some of the compounds are carbamic acid compounds having a substituted phenylacylamido group (-NHCOPh) linked to a carbamic acid (-CONHOH) group via a long alkylene chain, $-(CH_2)_n-$, wherein n is from 4 to 8

Some of the compounds are carbamic acid compounds having a substituted phenylamido group (-CONHPh) or phenylacylamido group (-NHCOPh) linked to a carbamic acid (-CONHOH) group via a long alkylene chain, $-(CH_2)_n-$, wherein n is from 4 to 8 (see, for example, columns 7 and 13 of Breslow et al., 1997), or via a

phenylene group (see, for example, columns 24, 30-31 and compounds 20-55 in Table 1 of Breslow et al., 1997).

One of the compounds is a carbamic acid compound having benzylamido group (-$CONHCH_2Ph$) linked to a carbamic acid group (-CONHOH) via a -$(CH_2)_6$- group (see, for example, compound 19 in Table 1, at column 37 of Breslow et al., 1997).

Jung et al., 1997, 1999, describe several aromatic hydroxamic acid compounds which apparently inhibit HDAC. Some of the compounds have a phenylamido group (PhCONH-). One compound, a peptide analog, is shown below (see, e.g., compound 6 in Jung et al., 1997; compound 4 in Jung et al., 1999).



Kato et al., 1998, describe a number of aromatic hydroxamic acid compounds, comprising an aryl group linked via an alkylene group to a carbamic acid group, which are apparently active in the treatment of neurodegenerative conditions. One compound, 4-1 at columns 63-64, has a phenylamido group (PhCONH-) linked via a -$(CH_2)_5$- group to a carbamic acid group.

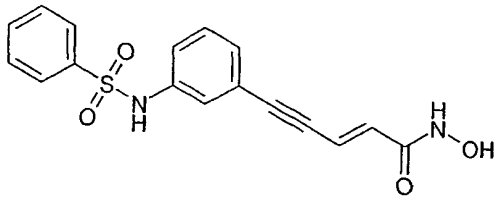
Glick et al., 1999, describe the apparent apoptotic and differentiating effects of m-carboxy-cinnamic acid bishydroxamide (CBHA) on various tumour cell lines.

Massa et al., 2001, describe various hydroxamic acid compounds which have a benzoyl (or substituted benzoyl) group linked via a pyrrolyl group and an C_2alkylene group (-CH=CH- or -CH_2CH_2-) to a carbamic acid group. The compounds apparently showed HDAC inhibitory activity in the micromolar range.

Sulfonamides

Oxamflatin, also known as (2E)-5-[3-[(phenylsulfonyl)amino] phenyl]-pent-2-en-4-ynohydroxamic acid, shown below, has been reported to have *in vitro* antiproliferative activity against various mouse and human tumour cell lines, and *in vivo* antitumour activity against B16 melanoma (see, e.g., Sonoda et al., 1996; Kim et al., 1999).

Oxamflatin



Ohtani et al., 1993, describe a number of hydroxamic acid compounds which are claimed to be inhibitors of ras transformation. Many of the compounds are hydroxmic acid compounds which have a sulfonamide group, and which employ an acid leader which is: a phenylene-ortho-alkylene (e.g., I-10); phenylene-meta-alkylene (e.g., I-24); phenylene-para-alkylene (e.g., I-12); or napthylen-1,2-diyl (e.g., I-20). However, in every case, the sulfonamide group is $-SO_2NR-$, as opposed to $-NRSO_2-$. Also, in every case, the terminal aryl group is linked directly to the $-SO_2NR-$ sulfonamide group, without an intervening aryl leader. Ohtani et al., 1996, describe similar compounds.

Richon et al., 2001, describe various branched compounds which apparently inhibit histone deacetylase. See the table at pages 96-101 therein. Some of the compounds are carbamic acid compounds having a carbamic acid group (-CONHOH) linked to a branch point, from which two aryl groups are appended. A few linear carbamic acid compounds are also described, including a single $-SO_2NH-$ sulfonamide carbamic acid with a $-(CH_2)_5-$ acid leader (compound 671).

Delorme et al., 2001, describe various carbamic acid compounds, including compounds having, inter alia, a sulfonamide group. Of the 108 compounds in the table at pages 114-123 therein, 88 are carbamic acids (-CONHOH), and the

remainder are terminal amides, -CONHR. Of the 88 carbamic acid compounds, 54 have a sulfonamide linkage.

Of the 54 sulfonamide carbamic acids, 51 are indicated to have a $-SO_2NR-$ sulfonamide group, and 3 (compounds 98, 161, and 162) are indicated to have a $-NRSO_2-$ sulfonamide group.

All of the 54 sulfonamide carbamic acids employ a phenylene-alkylene acid leader group (analogous to Q^2 herein). Of the 54 compounds, 52 employ a phenylene-para-alkylene group, and only 2 (compounds 41 and 26) employ a phenylene-meta-alkylene group ($-Ph-CH_2-$ and $-Ph-(CH_2)_4-$, respectively). Compounds 41 and 26 both have a $-SO_2NR-$ sulfonamide group, as opposed to a $-NRSO_2-$ sulfonamide group; the former has a benzothiophenyl group, and the latter has a phenyl group.

All but one of the 54 sulfonamide carbamic acids have an aryl group linked directly to the sulfonamide; compound 100 has a benzyl group ($Ph-CH_2-$) linked a $-SO_2NR-$ sulfonamide group linked to phenylene-para-ethylene.

SUMMARY OF THE INVENTION

One aspect of the invention pertains to active carbamic acid compounds, as described herein, which inhibit HDAC activity.

Another aspect of the invention pertains to active compounds, as described herein, which treat a proliferative condition, such as cancer or psoriasis.

Another aspect of the invention pertains to active compounds, as described herein, which treat conditions which are known to be mediated by HDAC, or which are known to be treated by HDAC inhibitors (such as, e.g., trichostatin A).

Another aspect of the present invention pertains to a composition comprising a compound as described herein and a pharmaceutically acceptable carrier.

Another aspect of the present invention pertains to methods of inhibiting HDAC in a cell, comprising contacting said cell with an effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to methods of inhibiting cell proliferation, comprising contacting a cell with an effective amount of an active compound, as described herein, whether *in vitro* or *in vivo*.

Another aspect of the present invention pertains to methods of treating a proliferative condition in a patient comprising administering to said patient a therapeutically-effective amount of an active compound, as described herein. In one preferred embodiment, the proliferative condition is cancer. In one preferred embodiment, the proliferative condition is psoriasis.

Another aspect of the present invention pertains to methods of treating a condition in a patient which is known to be mediated by HDAC, or which is known to be treated by HDAC inhibitors (such as, e.g., trichostatin A), comprising administering to said patient a therapeutically-effective amount of an active compound, as described herein.

Another aspect of the present invention pertains to an active compound, as described herein, for use in a method of treatment of the human or animal body.

Another aspect of the present invention pertains to use of an active compound, as described herein, for the manufacture of a medicament for use in the treatment of a proliferative condition. In one preferred embodiment, the proliferative condition is cancer. In one preferred embodiment, the proliferative condition is psoriasis.

Another aspect of the present invention pertains to use of an active compound for the manufacture of a medicament, for example, for the treatment of conditions which are known to be mediated by HDAC, or which are known to be treated by HDAC inhibitors (such as, e.g., trichostatin A), as discussed herein.

Another aspect of the present invention pertains to a kit comprising (a) the active compound, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the active compound.

Another aspect of the present invention pertains to compounds obtainable by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to compounds obtained by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to novel intermediates, as described herein, which are suitable for use in the methods of synthesis described herein.

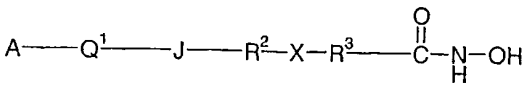
Another aspect of the present invention pertains to the use of such novel intermediates, as described herein, in the methods of synthesis described herein.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Compounds

In one embodiment, the present invention pertains to carbamic acid compounds of the formula:



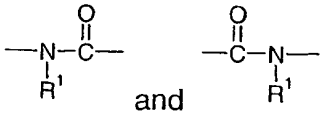
(1)

wherein:

A is an aryl group;

Q^1 is a covalent bond or an aryl leader group;

J is an amide linkage selected from:



and

R^1 is an amido substituent;

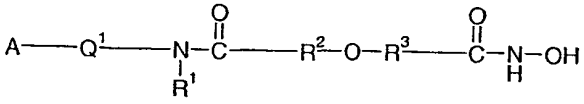
X is an ether heteroatom, and is -O- or -S-; and,

R^2 and R^3 are each independently an ether group;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

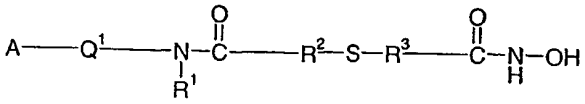
In preferred embodiments, the carbamic acid group, -C(=O)NHOH, is unmodified (e.g., is not an ester).

In one preferred embodiment, J is $-NR^1CO-$ and X is -O-, and the compounds have the following formula:



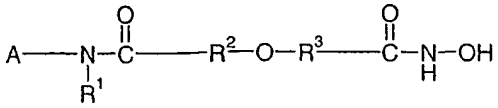
(2)

In one preferred embodiment, J is $-NR^1CO-$ and X is -S-, and the compounds have the following formula:



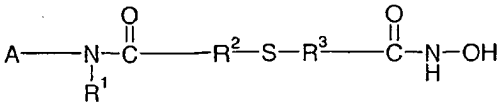
(3)

In one preferred embodiment, Q^1 is a covalent bond, J is $-NR^1CO-$ and X is -O-, and the compounds have the following formula:



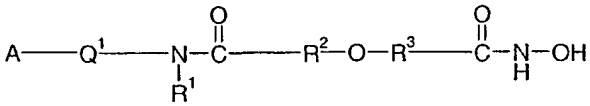
(4)

In one preferred embodiment, Q^1 is a covalent bond, J is $-NR^1CO-$ and X is -S-, and the compounds have the following formula:



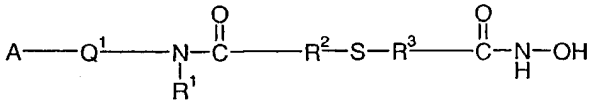
(5)

In one preferred embodiment, Q^1 is an aryl leader group, J is $-NR^1CO-$ and X is -O-, and the compounds have the following formula:



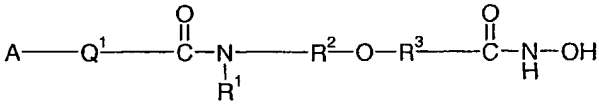
(6)

In one preferred embodiment, Q^1 is an aryl leader group, J is $-NR^1CO-$ and X is -S-, and the compounds have the following formula:



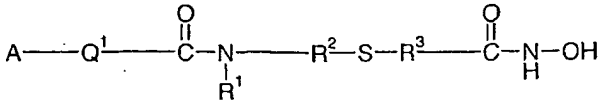
(7)

In one preferred embodiment, J is $-CONR^1-$ and X is -O-, and the compounds have the following formula:



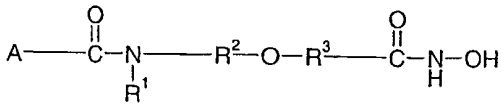
(8)

In one preferred embodiment, J is $-CONR^1-$ and X is -S-, and the compounds have the following formula:



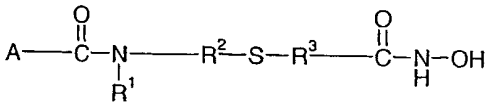
(9)

In one preferred embodiment, Q^1 is a covalent bond, J is $-CONR^1-$ and X is -O-, and the compounds have the following formula:



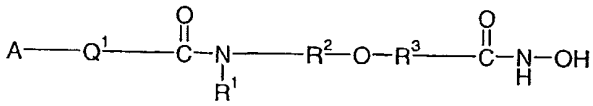
(10)

In one preferred embodiment, Q^1 is a covalent bond, J is $-CONR^1-$ and X is -S-, and the compounds have the following formula:



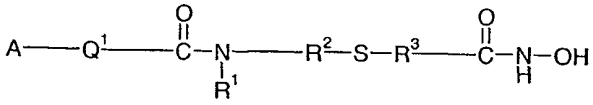
(11)

In one preferred embodiment, Q^1 is an aryl leader group, J is $-CONR^1-$ and X is -O-, and the compounds have the following formula:



(12)

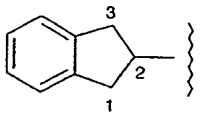
In one preferred embodiment, Q^1 is an aryl leader group, J is $-CONR^1-$ and X is -S-, and the compounds have the following formula:



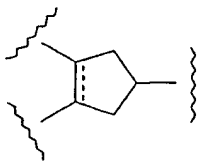
(13)

In one embodiment, where Q^1 is an aryl leader, the aryl group, A, is linked to Q^1 via a covalent single bond.

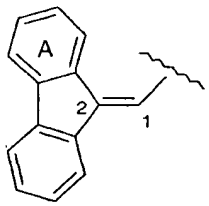
In one embodiment, where Q^1 is a cyclic aryl leader, the aryl group, A, may be fused to Q^1 and so the moiety $A-Q^1-$ forms a fused polycyclic structure. For example, the moiety 2,3-dihydro-1H-indene-2-yl, derived from indan (2,3-dihydro-1H-indene), is considered to be a phenyl group (A) fused to a C_5cycloalkyl group (Q^1):



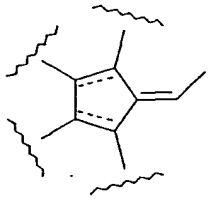
In such cases, the tridentate aryl leader, Q^1, may be denoted as:



In a similar example, the moiety 9H-fluorene-9-yl, derived from fluorene, is considered to be two phenyl groups (either of which is A), fused to a C_5cycloalkyl group, which forms part of Q^1:



In such cases, the pentadentate aryl leader, Q^1, may be denoted as:



The Aryl Group, A

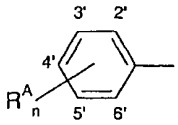
The aryl group, A, is a C_{5-20}aryl group, and is optionally substituted.

In one preferred embodiment, A is a C_{5-20}heteroaryl group, and is optionally substituted. In one preferred embodiment, A is a monocyclic C_{5-20}heteroaryl group, and is optionally substituted. In one preferred embodiment, A is a monocyclic C_{5-6}heteroaryl group, and is optionally substituted.

In one preferred embodiment, A is a C_{5-20}carboaryl group, and is optionally substituted. In one preferred embodiment, A is a monocyclic C_{5-20}carboaryl group, and is optionally substituted. In one preferred embodiment, A is a monocyclic C_{5-6}carboaryl group, and is optionally substituted. In one preferred embodiment, A is a phenyl group, and is optionally substituted.

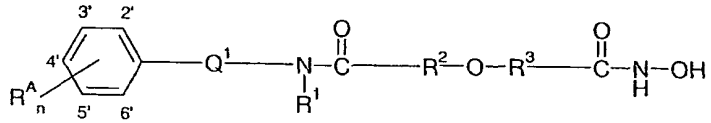
In one preferred embodiment, A is a C_{5-20}aryl group derived from one of the following: benzene, pyridine, furan, indole, pyrrole, imidazole, naphthalene, quinoline, benzimidazole, benzothiofuran, fluorene, acridine, and carbazole.

In one preferred embodiment, A is an optionally substituted phenyl group of the formula:



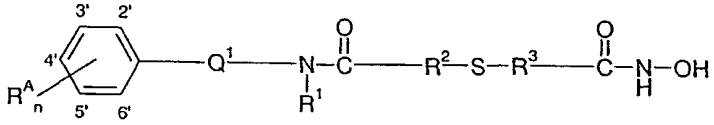
wherein n is an integer from 0 to 5, and each R^A is independently a substituent as defined herein.

In one preferred embodiment, A is an optionally substituted phenyl group, J is $-NR^1CO-$ and X is -O-, and the compounds have the following formula:



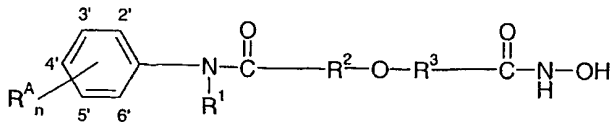
(14)

In one preferred embodiment, A is an optionally substituted phenyl group, J is $-NR^1CO-$ and X is -S-, and the compounds have the following formula:



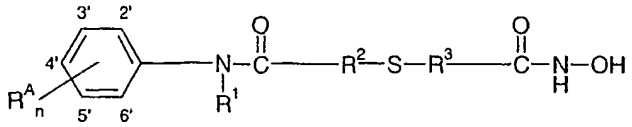
(15)

In one preferred embodiment, A is an optionally substituted phenyl group, Q^1 is a covalent bond, J is $-NR^1CO-$ and X is -O-, and the compounds have the following formula:



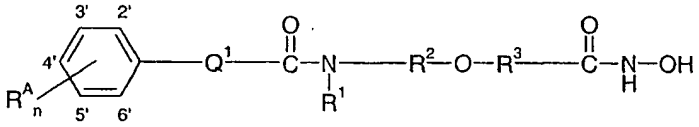
(16)

In one preferred embodiment, A is an optionally substituted phenyl group, Q^1 is a covalent bond, J is $-NR^1CO-$ and X is -S-, and the compounds have the following formula:



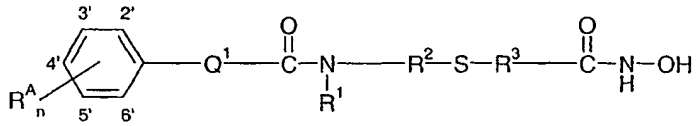
(17)

In one preferred embodiment, A is an optionally substituted phenyl group, J is $-CONR^1-$ and X is -O-, and the compounds have the following formula:



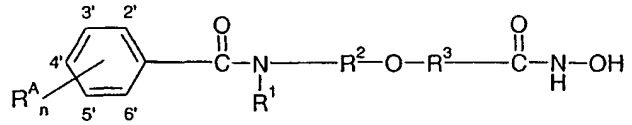
(18)

In one preferred embodiment, A is an optionally substituted phenyl group, J is $-CONR^1-$ and X is -S-, and the compounds have the following formula:



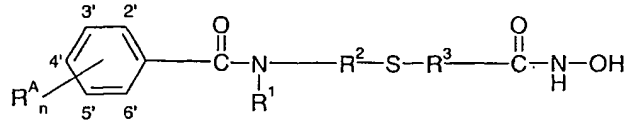
(19)

In one preferred embodiment, A is an optionally substituted phenyl group, Q^1 is a covalent bond, J is $-CONR^1-$ and X is -O-, and the compounds have the following formula:



(20)

In one preferred embodiment, A is an optionally substituted phenyl group, Q^1 is a covalent bond, J is $-CONR^1-$ and X is -S-, and the compounds have the following formula:



(21)

In one preferred embodiment, n is an integer from 0 to 5. In one preferred embodiment, n is an integer from 0 to 4. In one preferred embodiment, n is an integer from 0 to 3. In one preferred embodiment, n is an integer from 0 to 2. In one preferred embodiment, n is 0 or 1.

In one preferred embodiment, n is an integer from 1 to 5.

In one preferred embodiment, n is an integer from 1 to 4.

In one preferred embodiment, n is an integer from 1 to 3.

In one preferred embodiment, n is 1 or 2.

In one preferred embodiment, n is 5.

In one preferred embodiment, n is 4.

In one preferred embodiment, n is 3.

In one preferred embodiment, n is 2.

In one preferred embodiment, n is 1.

In one preferred embodiment, n is 0.

If the phenyl group has less than the full complement of ring substituents, R^A, they may be arranged in any combination. For example, if n is 1, R^A may be in the 2'-, 3'-, 4'-, 5'-, or 6'-position. Similarly, if n is 2, the two R^A groups may be in, for example, the 2',3'-, 2',4'-, 2',5'-, 2',6'-, 3',4'-, or 3',5'-positions. If n is 3, the three R^A groups may be in, for example, the 2',3',4'-, 2',3',5'-, 2',3',6'-, or 3',4',5'-positions.

In one preferred embodiment, n is 1, and the R^A group is in the 4'-position.

In one preferred embodiment, n is 2, and one R^A group is in the 4'-position, and the other R^A group is in the 2'-position.

In one preferred embodiment, n is 2, and one R^A group is in the 4'-position, and the other R^A group is in the 3'-position.

Each aryl substituent, R^A, is a substituent as defined herein.

Examples of preferred aryl substituents, R^A, include, but are not limited to, the following: fluoro, chloro, bromo, iodo, methyl, ethyl, isopropyl, t-butyl, cyano, trifluoromethyl, hydroxy, methoxy, ethoxy, isopropoxy, trifluoromethoxy, phenoxy, methylthio, trifluoromethylthio, hydroxymethyl, amino, dimethylamino, diethylamino, morpholino, amido (unsubstituted, i.e., $-CONH_2$), acetamido, acetyl, nitro, sulfonamido (unsubstituted, i.e., $-SO_2NH_2$), and phenyl.

In one preferred embodiment, A is a substituted phenyl group selected from:

para-(fluoro)phenyl; ortho-(fluoro)phenyl; meta-(fluoro)phenyl;
para-(chloro)phenyl; ortho-(chloro)phenyl; meta-(chloro)phenyl;
para-(bromo)phenyl; ortho-(bromo)phenyl; meta-(bromo)phenyl;
para-(iodo)phenyl; ortho-(iodo)phenyl; meta-(iodo)phenyl;
para-(methyl)phenyl; ortho-(methyl)phenyl; meta-(methyl)phenyl;
para-(ethyl)phenyl; ortho-(ethyl)phenyl; meta-(ethyl)phenyl;
para-(isopropyl)phenyl; ortho-(isopropyl)phenyl; meta-(isopropyl)phenyl;
para-(t-butyl)phenyl; ortho-(t-butyl)phenyl; meta-(t-butyl)phenyl;
para-(cyano)phenyl; ortho-(cyano)phenyl; meta-(cyano)phenyl;
para-(trifluoromethyl)phenyl; ortho-(trifluoromethyl)phenyl; meta-(trifluoromethyl)phenyl;
para-(hydroxy)phenyl; ortho-(hydroxy)phenyl; meta-(hydroxy)phenyl;
para-(methoxy)phenyl; ortho-(methoxy)phenyl; meta-(methoxy)phenyl;
para-(ethoxy)phenyl; ortho-(ethoxy)phenyl; meta-(ethoxy)phenyl;
para-(isopropoxy)phenyl; ortho-(isopropoxy)phenyl; meta-(isopropoxy)phenyl;
para-(trifluoromethoxy)phenyl; ortho-(trifluoromethoxy)phenyl; meta-(trifluoromethoxy)phenyl;
para-(phenoxy)phenyl; ortho-(phenoxy)phenyl; meta-(phenoxy)phenyl;
para-(methylthio)phenyl; ortho-(methylthio)phenyl; meta-(methylthio)phenyl;
para-(trifluoromethylthio)phenyl; ortho-(trifluoromethylthio)phenyl; meta-(trifluoromethylthio)phenyl;
para-(hydroxymethyl)phenyl; ortho-(hydroxymethyl)phenyl; meta-(hydroxymethyl)phenyl;
para-(amino)phenyl; ortho-(amino)phenyl; meta-(amino)phenyl;

para-(dimethylamino)phenyl; ortho-(dimethylamino)phenyl;
meta-(dimethylamino)phenyl;
para-(diethylamino)phenyl; ortho-(diethylamino)phenyl;
meta-(diethylamino)phenyl;
para-(morpholino)phenyl; ortho-(morpholino)phenyl;
meta-(morpholino)phenyl;
para-(amido)phenyl; ortho-(amido)phenyl; meta-(amido)phenyl;
para-(acetamido)phenyl; ortho-(acetamido)phenyl;
meta-(acetamido)phenyl;
para-(acetyl)phenyl; ortho-(acetyl)phenyl; meta-(acetyl)phenyl;
para-(nitro)phenyl; ortho-(nitro)phenyl; meta-(nitro)phenyl;
para-(sulfonamido)phenyl; ortho-(sulfonamido)phenyl;
meta-(sulfonamido)phenyl; and,
para-(phenyl)phenyl; ortho-(phenyl)phenyl; meta-(phenyl)phenyl.

In one preferred embodiment, A is a substituted phenyl group selected from:
para-(fluoro)phenyl;
para-(chloro)phenyl;
para-(bromo)phenyl;
para-(iodo)phenyl;
para-(methyl)phenyl;
para-(ethyl)phenyl;
para-(isopropyl)phenyl;
para-(t-butyl)phenyl;
para-(cyano)phenyl;
para-(trifluoromethyl)phenyl;
para-(hydroxy)phenyl;
para-(methoxy)phenyl;
para-(ethoxy)phenyl;
para-(isopropoxy)phenyl;
para-(trifluoromethoxy)phenyl;
para-(phenoxy)phenyl;
para-(methylthio)phenyl;

para-(trifluoromethylthio)phenyl;
para-(hydroxymethyl)phenyl;
para-(amino)phenyl;
para-(dimethylamino)phenyl;
para-(diethylamino)phenyl;
para-(morpholino)phenyl;
para-(amido)phenyl;
para-(acetamido)phenyl;
para-(acetyl)phenyl;
para-(nitro)phenyl;
para-(sulfonamido)phenyl; and,
para-(phenyl)phenyl.

In one preferred embodiment, A is a substituted phenyl group selected from:

ortho,para-di(methoxy)phenyl;
ortho,para-di(halo)phenyl;
ortho,para-di(fluoro)phenyl;
ortho-(methoxy),para-(methyl)phenyl;
ortho-(methoxy),para-(trifluoromethyl)phenyl;
ortho-(trifluoromethyl),para-(halo)phenyl;

ortho,meta-di(trifluoromethyl)phenyl;
ortho-(halo),meta-(trifluoromethyl)phenyl;

meta,para-di(halo)phenyl;
meta,para-di(hydroxy)phenyl;
meta,para-di(methyl)phenyl;
meta,para-di(methoxy)phenyl;
meta-(halo),para-(nitro)phenyl;

3',5'-di(trifluoromethyl)phenyl;
3'-(trifluoromethyl),5'-(methoxy)phenyl;

3'-(trifluoromethyl),5'-(halo)phenyl;

2'-(halo),5'-(methyl)phenyl;

2',6'-di(methyl)phenyl;
2',6'-di(halo)phenyl;
2',6'-di(isopropyl)phenyl;

2',4',6'-tri(halo)phenyl;
3',4',5'-tri(halo)phenyl;
3',4',5'-tri(methoxy)phenyl;
2',5'-di(halo)-4'-(hydroxy)phenyl; and
3'-(trifluoromethyl),5',6'-di(halo)phenyl.

The Aryl Leader Group, Q^1

As mentioned above, in some embodiments, Q^1 is a covalent bond or an aryl leader group; in some embodiments, Q^1 is a covalent bond; in some embodiments, Q^1 is an aryl leader group.

In one preferred embodiment, Q^1 is a covalent bond.

In one preferred embodiment, Q^1 is a C_{1-7}alkylene group and is optionally substituted.

In one preferred embodiment, Q^1 is a covalent bond or a C_{1-7}alkylene group and is optionally substituted.

In one preferred embodiment, Q^1 is a covalent bond or a saturated C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a saturated C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a partially unsaturated C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a partially unsaturated C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or an aliphatic C_{1-7}alkylene group. In one preferred embodiment, Q^1 is an aliphatic C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a linear C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a linear C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a branched C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a branched C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or an alicyclic C_{1-7}alkylene group. In one preferred embodiment, Q^1 is an alicyclic C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a saturated aliphatic C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a saturated aliphatic C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a saturated linear C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a saturated linear C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a saturated branched C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a saturated branched C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a saturated alicyclic C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a saturated alicyclic C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a partially unsaturated aliphatic C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a partially unsaturated aliphatic C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a partially unsaturated linear C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a partially unsaturated linear C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a partially unsaturated branched C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a partially unsaturated branched C_{1-7}alkylene group.

In one preferred embodiment, Q^1 is a covalent bond or a partially unsaturated alicyclic C_{1-7}alkylene group. In one preferred embodiment, Q^1 is a partially unsaturated alicyclic C_{1-7}alkylene group.

Note that, as discussed below in the context of isomers, where unsaturation permits isomers, e.g., cis- and trans, E- and Z-, etc., and combinations thereof, a reference to one isomer is to be considered a reference to all such isomers, unless otherwise specified.

The Aryl Leader Group, Q^1: Substituents

In one embodiment, Q^1 is unsubstituted.
In one embodiment, Q^1 is optionally substituted.
In one embodiment, Q^1 is substituted.

Examples of substituents on Q^1 include, but are not limited to, those described under the heading "Substituents" below.

In one preferred embodiment, substituents on Q^1, if present, are independently selected from: halo, hydroxy, ether (e.g., C_{1-7}alkoxy), C_{5-20}aryl, acyl, amido, and oxo.

In one preferred embodiment, substituents on Q^1, if present, are independently selected from -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -OPr, -Ph, and =O.

In one preferred embodiment, substituents on Q^1, if present, are -OH or -Ph.

In one preferred embodiment, substituents on Q^1, if present, are -Ph.

For example, in one embodiment, Q^1 is unsubsituted ethylene, and is $-CH_2-CH_2-$; in one embodiment, Q^1 is oxo (=O) subsituted ethylene, and is $-C(=O)-CH_2-$; in one embodiment, Q^1 is hydroxy (-OH) subsituted ethylene, and is $-CH(OH)-CH_2-$; in one embodiment, Q^1 is phenyl (-Ph) substituted ethylene, and is $-CH_2CH(Ph)-$.

The Aryl Leader Group, Q^1: Certain Embodiments

Note that, for embodiments excluding, e.g., a covalent bond, certain backbone lengths, etc., it is to be understood that the corresponding species listed below are similarly excluded from the respective embodiments discussed below.

In one preferred embodiment, Q^1 is selected from the following:

a covalent bond;

$-(CH_2)_n-$ where n is an integer from 1 to 7;

$-CH(CH_3)-$;
$-CH(CH_3)CH_2-$ and $-CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH_2CH_2CH(CH_3)-$;

-$CH(CH_2CH_3)$-;

-$CH(CH_2CH_3)CH_2$- and -$CH_2CH(CH_2CH_3)$-;

-$CH(CH_2CH_3)CH_2CH_2$-, -$CH_2CH(CH_2CH_3)CH_2$-, and -$CH_2CH_2CH(CH_2CH_3)$-;

-$CH(CH_2CH_3)CH_2CH_2CH_2$-, -$CH_2CH(CH_2CH_3)CH_2CH_2$-, -$CH_2CH_2CH(CH_2CH_3)CH_2$-, and -$CH_2CH_2CH_2CH(CH_2CH_3)$-;

-$CH(CH_2CH_3)CH_2CH_2CH_2CH_2$-, -$CH_2CH(CH_2CH_3)CH_2CH_2CH_2$-, -$CH_2CH_2CH(CH_2CH_3)CH_2CH_2$-, -$CH_2CH_2CH_2CH(CH_2CH_3)CH_2$-, and -$CH_2CH_2CH_2CH_2CH(CH_2CH_3)$-;

-CH=CH-;

-$CH=CHCH_2$- and -$CH_2CH=CH$-;

-$CH=CHCH_2CH_2$-, -$CH_2CH=CHCH_2$-, and -$CH_2CH_2CH=CH$-;

-$CH=CHCH_2CH_2CH_2$-, -$CH_2CH=CHCH_2CH_2$-, -$CH_2CH_2CH=CHCH_2$-, and -$CH_2CH_2CH_2CH=CH$-;

-$CH=CHCH_2CH_2CH_2CH_2$-, -$CH_2CH=CHCH_2CH_2CH_2$-, -$CH_2CH_2CH=CHCH_2CH_2$-, -$CH_2CH_2CH_2CH=CHCH_2$-, and -$CH_2CH_2CH_2CH_2CH=CH$-;

-$C(CH_3)=CH$- and -$CH=C(CH_3)$-;

-$C(CH_3)=CHCH_2$-, -$CH=C(CH_3)CH_2$-, and -$CH=CHCH(CH_3)$-;

-$CH(CH_3)CH=CH$-, -$CH_2C(CH_3)=CH$-, and -$CH_2CH=C(CH_3)$-;

-CH=CHCH=CH-;

-$CH=CHCH=CHCH_2$-, -$CH_2CH=CHCH=CH$-, and -$CH=CHCH_2CH=CH$-;

-$CH=CHCH=CHCH_2CH_2$-, -$CH=CHCH_2CH=CHCH_2$-, -$CH=CHCH_2CH_2CH=CH$-, -$CH_2CH=CHCH=CHCH_2$-, -$CH_2CH=CHCH_2CH=CH$-, and -$CH_2CH_2CH=CHCH=CH$-;

-$C(CH_3)=CHCH=CH$-, -$CH=C(CH_3)CH=CH$-, -$CH=CHC(CH_3)=CH$-, and -$CH=CHCH=C(CH_3)$-;

-C≡C-;

$-C\equiv CCH_2-$, $-CH_2C\equiv C-$; $-C\equiv CCH(CH_3)-$, and $-CH(CH_3)C\equiv C-$;

$-C\equiv CCH_2CH_2-$, $-CH_2C\equiv CCH_2-$, and $-CH_2CH_2C\equiv C-$;

$-C\equiv CCH(CH_3)CH_2-$ and $-C\equiv CCH_2CH(CH_3)-$;

$-CH(CH_3)C\equiv CCH_2-$ and $-CH_2C\equiv CCH(CH_3)-$;

$-CH(CH_3)CH_2C\equiv C-$ and $-CH_2CH(CH_3)C\equiv C-$;

$-C\equiv CCH=CH-$, $-CH=CHC\equiv C-$, and $-C\equiv CC\equiv C-$;

$-C\equiv CCH_2CH_2CH_2-$ and $-CH_2CH_2CH_2C\equiv C-$;

$-C\equiv CCH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2C\equiv C-$;

$-C\equiv CCH=CHCH=CH-$, $-CH=CHC\equiv C-CH=CH-$, and $-CH=CHCH=CHC\equiv C-$;

$-C(CH_3)=CHC\equiv C-$, $-CH=C(CH_3)C\equiv C-$, $-C\equiv CC(CH_3)=CH-$, and $-C\equiv CCH=C(CH_3)-$;

cyclopentylene and cyclopentenylene; and,

cyclohexylene, cyclohexenylene, and cyclohexadienylene.

In one preferred embodiment, Q^1 is selected from:

a covalent bond;

$-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, and $-(CH_2)_6-$;

$-CH(CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH_2CH_2CH(CH_3)-$;

$-CH=CH-$;

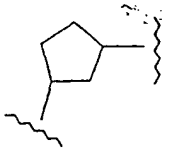
$-CH=CH-CH=CH-$;

$-CH=CHCH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH=CH-$;

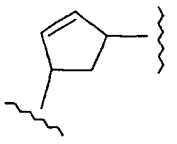
$-CH=CHCH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2CH=CH-$;

$-C(CH_3)=CHCH=CH-$, $-CH=C(CH_3)CH=CH-$, $-CH=CHC(CH_3)=CH-$, and $-CH=CHCH=C(CH_3)-$;

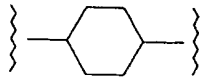
(cyclopent-1,3-ylene)



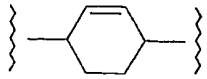
(4-cyclopenten-1,3-ylene)



(cyclohex-1,4-ylene)



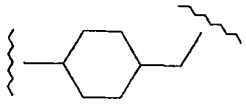
(2-cyclohexen-1,4-ylene)



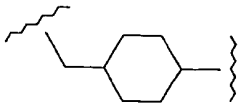
(2,5-cyclohexadien-1,4-ylene)



(cyclohex-1,4-ylene-methylene)



(methylene-cyclohex-1,4-ylene)



In one preferred embodiment, Q^1 is selected from:

a covalent bond;

$-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$,

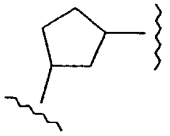
$-CH=CH-$;

$-CH=CH-CH=CH-$;

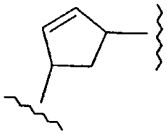
$-C(CH_3)=CHCH=CH-$, $-CH=C(CH_3)CH=CH-$, $-CH=CHC(CH_3)=CH-$, and $-CH=CHCH=C(CH_3)-$;

$-CH=CHCH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH=CH-$; and,

(cyclopent-1,3-ylene)



(4-cyclopenten-1,3-ylene)



In one preferred embodiment, Q^1 is selected from: a covalent bond, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, and $-CH=CH-CH=CH-$.

In one preferred embodiment, Q^1 is selected from:

a covalent bond, $-CH_2-$, $-CH=CH-$, and $-CH=CH-CH=CH-$.

In one preferred embodiment, Q^1 is selected from:

$-CH_2-$, $-CH=CH-$, and $-CH=CH-CH=CH-$.

The Amido Substituent, R^1

The amido substituent, R^1, is hydrogen, C_{1-7}alkyl (including, e.g., C_{5-20}aryl-C_{1-7}alkyl), C_{3-20}heterocyclyl, or C_{5-20}aryl.

Note that R^1 is a monodentate species. It is not intended that R^1 be additionally linked to A, Q^1, and/or Q^2, thereby forming a cyclic group.

In one preferred embodiment, R^1 is hydrogen, C_{1-7}alkyl, or C_{5-20}aryl.
In one preferred embodiment, R^1 is hydrogen or C_{1-7}alkyl.

In one preferred embodiment, R^1 is hydrogen, saturated C_{1-7}alkyl, or C_{5-20}aryl.
In one preferred embodiment, R^1 is hydrogen or saturated C_{1-7}alkyl.

In one preferred embodiment, R^1 is hydrogen, saturated aliphatic C_{1-7}alkyl, or C_{5-20}aryl.
In one preferred embodiment, R^1 is hydrogen or saturated aliphatic C_{1-7}alkyl.

In one preferred embodiment, R^1 is -H, -Me, -Et, -nPr, -iPr, -nBu, -sBu, -tBu, -Ph, or -Bn.
In one preferred embodiment, R^1 is -H, -Me, -Et, -nPr, -iPr, -nBu, -sBu, or -tBu.

In one preferred embodiment, R^1 is -H, -Me, -Et, -Ph, or -Bn.
In one preferred embodiment, R^1 is -H, -Me, or -Et.

In one preferred embodiment, R^1 is -H.

The Ether Groups, R^2 and R^3

Each of the ether groups, R^2 and R^3, is independently C_{1-7}alkylene; C_{5-20}arylene; C_{5-20}arylene-C_{1-7}alkylene; or C_{1-7}alkylene-C_{5-20}arylene; and is optionally substituted.

In one preferred embodiment, each of the ether groups, R^2 and R^3, is independently a C_{1-7}alkylene group, and is optionally substituted.

In one embodiment, each of R^2 and R^3 is unsubstituted.
In one embodiment, each of R^2 and R^3 is optionally substituted.
In one embodiment, each of R^2 and R^3 is substituted.

The Ether Groups, R^2 and R^3: Alkylene

In one preferred embodiment, R^2 and/or R^3 is a saturated C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a partially unsaturated C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is an aliphatic C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a linear C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a branched C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is an alicyclic C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a saturated aliphatic C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a saturated linear C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a saturated branched C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a saturated alicyclic C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a partially unsaturated aliphatic C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a partially unsaturated linear C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a partially unsaturated branched C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is a partially unsaturated alicyclic C_{1-7}alkylene group.

In one preferred embodiment, R^2 and/or R^3 is selected from:

$-(CH_2)_n-$ where n is an integer from 1 to 7;

$-CH(CH_3)-$;
$-CH(CH_3)CH_2-$ and $-CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH_2CH_2CH(CH_3)-$;

$-CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2-$ and $-CH_2CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2-$, and $-CH_2CH_2CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_2CH_3)CH_2-$, and $-CH_2CH_2CH_2CH(CH_2CH_3)-$;

$-CH(CH_2CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_2CH_3)CH_2-$, and $-CH_2CH_2CH_2CH_2CH(CH_2CH_3)-$;

$-CH=CH-$;

$-CH=CHCH_2-$ and $-CH_2CH=CH-$;

$-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, and $-CH_2CH_2CH=CH-$;

$-CH=CHCH_2CH_2CH_2-$, $-CH_2CH=CHCH_2CH_2-$, $-CH_2CH_2CH=CHCH_2-$, and $-CH_2CH_2CH_2CH=CH-$;

$-CH=CHCH_2CH_2CH_2CH_2-$, $-CH_2CH=CHCH_2CH_2CH_2-$, $-CH_2CH_2CH=CHCH_2CH_2-$, $-CH_2CH_2CH_2CH=CHCH_2-$, and $-CH_2CH_2CH_2CH_2CH=CH-$;

$-C(CH_3)=CH-$ and $-CH=C(CH_3)-$;

$-C(CH_3)=CHCH_2-$, $-CH=C(CH_3)CH_2-$, and $-CH=CHCH(CH_3)-$;

$-CH(CH_3)CH=CH-$, $-CH_2C(CH_3)=CH-$, and $-CH_2CH=C(CH_3)-$;

$-CH=CHCH=CH-$;

$-CH=CHCH=CHCH_2-$, $-CH_2CH=CHCH=CH-$, and $-CH=CHCH_2CH=CH-$;

$-CH=CHCH=CHCH_2CH_2-$, $-CH=CHCH_2CH=CHCH_2-$, and $-CH=CHCH_2CH_2CH=CH-$, $-CH_2CH=CHCH=CHCH_2-$, $-CH_2CH=CHCH_2CH=CH-$, and $-CH_2CH_2CH=CHCH=CH-$;

cyclopentylene and cyclopentenylene; and,

cyclohexylene, cyclohexenylene, and cyclohexadienylene.

In one preferred embodiment, R^2 and/or R^3 is selected from:

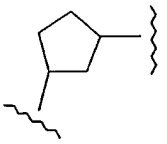
$-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, and $-(CH_2)_6-$;

$-CH(CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH_2CH_2CH(CH_3)-$;

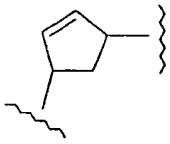
$-CH=CHCH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH=CH-$;

$-CH=CHCH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2CH=CH-$;

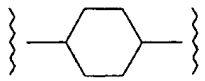
(cyclopent-1,3-ylene)



(4-cyclopenten-1,3-ylene)



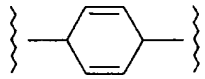
(cyclohex-1,4-ylene)



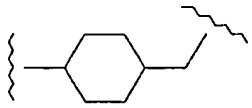
(2-cyclohexen-1,4-ylene)



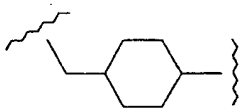
(2,5-cyclohexadien-1,4-ylene)



(cyclohex-1,4-ylene-methylene)



(methylene-cyclohex-1,4-ylene)



In one preferred embodiment, each of R^2 and R^3 is a saturated C_{1-7}alkylene group.

In one preferred embodiment, each of R^2 and R^3 is selected from $-(CH_2)_n-$, wherein n is an integer from 1 to 5.

In one preferred embodiment, the group R^2-X-R^3 is selected from the following:

$-CH_2-O-CH_2-$ and $-CH_2-S-CH_2-$;

$-CH_2-O-CH_2CH_2-$ and $-CH_2-S-CH_2CH_2-$;

$-CH_2CH_2-O-CH_2-$ and $-CH_2CH_2-S-CH_2-$;

$-CH_2-O-CH_2CH_2CH_2-$ and $-CH_2-S-CH_2CH_2CH_2-$;

$-CH_2CH_2-O-CH_2CH_2-$ and $-CH_2CH_2-S-CH_2CH_2-$;

$-CH_2CH_2CH_2-O-CH_2-$ and $-CH_2CH_2CH_2-S-CH_2-$;

$-CH_2-O-CH_2CH_2CH_2CH_2-$ and $-CH_2-S-CH_2CH_2CH_2CH_2-$;

$-CH_2CH_2-O-CH_2CH_2CH_2-$ and $-CH_2CH_2-S-CH_2CH_2CH_2-$;

$-CH_2CH_2CH_2-O-CH_2CH_2-$ and $-CH_2CH_2CH_2-S-CH_2CH_2-$;

$-CH_2CH_2CH_2CH_2-O-CH_2-$ and $-CH_2CH_2CH_2CH_2-S-CH_2-$;

$-CH_2-O-CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2-S-CH_2CH_2CH_2CH_2CH_2-$;

$-CH_2CH_2-O-CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2-S-CH_2CH_2CH_2CH_2-$;

$-CH_2CH_2CH_2-O-CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2-S-CH_2CH_2CH_2-$;

$-CH_2CH_2CH_2CH_2-O-CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2-S-CH_2CH_2-$;

$-CH_2CH_2CH_2CH_2CH_2-O-CH_2-$ and $-CH_2CH_2CH_2CH_2CH_2-S-CH_2-$;

In one preferred embodiment, the group R^2-X-R^3 is selected from the following:

$-CH_2-O-CH_2-$ and $-CH_2-S-CH_2-$.

In one preferred embodiment, the group R^2-X-R^3 is selected from the following:

$-CH_2-O-CH_2CH_2-$ and $-CH_2-S-CH_2CH_2-$;

$-CH_2CH_2-O-CH_2-$ and $-CH_2CH_2-S-CH_2-$.

In one preferred embodiment, the group R^2-X-R^3 is selected from the following:

$-CH_2-O-CH_2CH_2CH_2-$ and $-CH_2-S-CH_2CH_2CH_2-$;

$-CH_2CH_2-O-CH_2CH_2-$ and $-CH_2CH_2-S-CH_2CH_2-$;

$-CH_2CH_2CH_2-O-CH_2-$ and $-CH_2CH_2CH_2-S-CH_2-$.

In one preferred embodiment, the group R^2-X-R^3 is selected from the following:

$-CH_2-O-CH_2CH_2CH_2CH_2-$ and $-CH_2-S-CH_2CH_2CH_2CH_2-$;

$-CH_2CH_2-O-CH_2CH_2CH_2-$ and $-CH_2CH_2-S-CH_2CH_2CH_2-$;

$-CH_2CH_2CH_2-O-CH_2CH_2-$ and $-CH_2CH_2CH_2-S-CH_2CH_2-$;

$-CH_2CH_2CH_2CH_2-O-CH_2-$ and $-CH_2CH_2CH_2CH_2-S-CH_2-$.

In one preferred embodiment, the group R^2-X-R^3 is selected from the following:

$-CH_2-O-CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2-S-CH_2CH_2CH_2CH_2CH_2-$;

$-CH_2CH_2-O-CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2-S-CH_2CH_2CH_2CH_2-$;

$-CH_2CH_2CH_2-O-CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2-S-CH_2CH_2CH_2-$;

$-CH_2CH_2CH_2CH_2-O-CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2-S-CH_2CH_2-$;

$-CH_2CH_2CH_2CH_2CH_2-O-CH_2-$ and $-CH_2CH_2CH_2CH_2CH_2-S-CH_2-$.

<u>The Ether Groups, R^2 and R^3: Arylene</u>

In one preferred embodiment, R^2 and/or R^3 is C_{5-20}arylene, and is optionally substituted.

In one preferred embodiment, R^2 and/or R^3 is C_{5-20}arylene. In one preferred embodiment, R^2 and/or R^3 is C_{5-6}arylene. In one preferred embodiment, R^2 and/or R^3 is phenylene.

The Ether Groups, R^2 and R^3: Alkylene-Arylene and Arylene-Alkylene

In one preferred embodiment, R^2 and/or R^3 is C_{5-20}arylene-C_{1-7}alkylene or C_{1-7}alkylene-C_{5-20}arylene, and is optionally substituted.

In one preferred embodiment, R^2 and/or R^3 is C_{5-6}arylene-C_{1-7}alkylene or C_{1-7}alkylene-C_{5-6}arylene, and is optionally substituted.

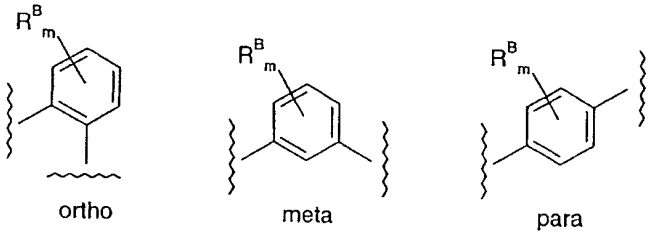
In one preferred embodiment, R^2 and/or R^3 is C_{1-7}alkylene-C_{5-20}arylene.
In one preferred embodiment, R^2 and/or R^3 is C_{1-7}alkylene-C_{5-6}arylene.

In one preferred embodiment, R^2 and/or R^3 is C_{5-20}arylene-C_{1-7}alkylene.
In one preferred embodiment, R^2 and/or R^3 is C_{5-6}arylene-C_{1-7}alkylene.

In one preferred embodiment, R^2 and/or R^3 is C_{1-7}alkylene-phenylene. In one preferred embodiment, R^2 and/or R^3 is methylene-phenylene, ethylene-phenylene, propylene-phenylene, and ethenylene-phenylene (also known as vinylene-phenylene).

In one preferred embodiment, R^2 and/or R^3 is phenylene-C_{1-7}alkylene. In one preferred embodiment, R^2 and/or R^3 is phenylene-methylene, phenylene-ethylene, phenylene-propylene, or phenylene-ethenylene (also known as phenylene-vinylene).

In the above alkylene-phenylene and phenylene-alkylene groups, the phenylene linkage may be ortho, meta, or para, and the phenylene group is optionally substituted with from 1 to 4 aryl substituents, R^B:



ortho meta para

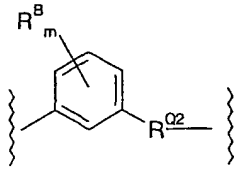
In one preferred embodiment, the phenylene linkage is meta or para. In one preferred embodiment, the phenylene linkage is para. In one preferred embodiment, the phenylene linkage is meta.

In one preferred embodiment, m is an integer from 0 to 4.
In one preferred embodiment, m is an integer from 0 to 3.
In one preferred embodiment, m is an integer from 0 to 2.
In one preferred embodiment, m is 0 or 1.
In one preferred embodiment, m is an integer from 1 to 4.
In one preferred embodiment, m is an integer from 1 to 3.
In one preferred embodiment, m is 1 or 2.
In one preferred embodiment, m is 4.
In one preferred embodiment, m is 3.
In one preferred embodiment, m is 2.
In one preferred embodiment, m is 1.
In one preferred embodiment, m is 0.

Each aryl substituent, R^B, is a substituent as defined herein.

Examples of preferred aryl substituents, R^B, include, but are not limited to, the following: fluoro, chloro, methyl, ethyl, isopropyl, t-butyl, trifluoromethyl, hydroxy, methoxy, ethoxy, isopropoxy, methylthio, amino, dimethylamino, diethylamino, morpholino, acetamido, nitro, and phenyl.

In one preferred embodiment, the phenylene linkage is meta, and R^2 and/or R^3 has the following formula, wherein R^{Q2} is C_{1-7}alkylene and is optionally substituted (referred to herein as "phenylene-meta-C_{1-7}alkylene"):



In one preferred embodiment, R^{Q2} is a saturated C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a partially unsaturated C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is an aliphatic C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a linear C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a branched C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is an alicyclic C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a saturated aliphatic C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a saturated linear C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a saturated branched C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a saturated alicyclic C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a partially unsaturated aliphatic C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a partially unsaturated linear C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a partially unsaturated branched C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is a partially unsaturated alicyclic C_{1-7}alkylene group.

In one preferred embodiment, R^{Q2} is selected from:

$-(CH_2)_n-$ where n is an integer from 1 to 7;
$-CH(CH_3)-$;
$-CH(CH_3)CH_2-$ and $-CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH_2CH(CH_3)-$;
$-CH(CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_3)CH_2-$, and $-CH_2CH_2CH_2CH_2CH(CH_3)-$;

$-CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2-$ and $-CH_2CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2-$, and $-CH_2CH_2CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH_2CH(CH_2CH_3)CH_2-$, and $-CH_2CH_2CH_2CH(CH_2CH_3)-$;
$-CH(CH_2CH_3)CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_2CH_3)CH_2CH_2CH_2-$, $-CH_2CH_2CH(CH_2CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH(CH_2CH_3)CH_2-$, and $-CH_2CH_2CH_2CH_2CH(CH_2CH_3)-$;

$-CH=CH-$;
$-CH=CHCH_2-$ and $-CH_2CH=CH-$;
$-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, and $-CH_2CH_2CH=CH-$;
$-CH=CHCH_2CH_2CH_2-$, $-CH_2CH=CHCH_2CH_2-$, $-CH_2CH_2CH=CHCH_2-$, and $-CH_2CH_2CH_2CH=CH-$;

-CH=CHCH$_2$CH$_2$CH$_2$CH$_2$-, -CH$_2$CH=CHCH$_2$CH$_2$CH$_2$-, -CH$_2$CH$_2$CH=CHCH$_2$CH$_2$-, -CH$_2$CH$_2$CH$_2$CH=CHCH$_2$-, and -CH$_2$CH$_2$CH$_2$CH$_2$CH=CH-;

-C(CH$_3$)=CH- and -CH=C(CH$_3$)-;

-C(CH$_3$)=CHCH$_2$-, -CH=C(CH$_3$)CH$_2$-, and -CH=CHCH(CH$_3$)-;

-CH(CH$_3$)CH=CH-, -CH$_2$C(CH$_3$)=CH-, and -CH$_2$CH=C(CH$_3$)-;

-CH=CHCH=CH-;

-CH=CHCH=CHCH$_2$-, -CH$_2$CH=CHCH=CH-, and -CH=CHCH$_2$CH=CH-;

-CH=CHCH=CHCH$_2$CH$_2$-, -CH=CHCH$_2$CH=CHCH$_2$-, and -CH=CHCH$_2$CH$_2$CH=CH-, -CH$_2$CH=CHCH=CHCH$_2$-, -CH$_2$CH=CHCH$_2$CH=CH-, and -CH$_2$CH$_2$CH=CHCH=CH-;

-C(CH$_3$)=CHCH=CH-, -CH=C(CH$_3$)CH=CH-, -CH=CHC(CH$_3$)=CH-, and -CH=CHCH=C(CH$_3$)-;

cyclopentylene and cyclopentenylene; and,

cyclohexylene, cyclohexenylene, and cyclohexadienylene.

In one preferred embodiment, R^{Q2} is selected from:

-CH$_2$-, -(CH$_2$)$_2$-, -(CH$_2$)$_3$-, -(CH$_2$)$_4$-, -(CH$_2$)$_5$-, and -(CH$_2$)$_6$-;

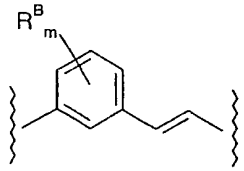
-CH=CH-, -CH=CH-CH=CH-;

In one preferred embodiment, R^{Q2} is cis or trans -CH=CH-.

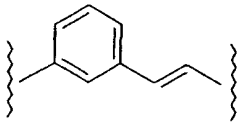
In one preferred embodiment, R^{Q2} is cis -CH=CH-.

In one preferred embodiment, R^{Q2} is trans -CH=CH-.

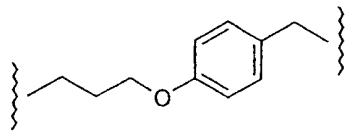
In one preferred embodiment, R^{Q2} is -CH=CH-, and R^2 and/or R^3 is (referred to herein as "phenylene-meta-trans-ethylene"):



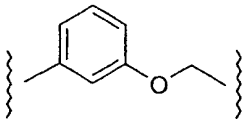
In one preferred embodiment, m is 0, and R^2 and/or R^3 is (referred to herein as "unsubstituted phenylene-meta-trans-ethylene"):



In one preferred embodiment, $-R^2-X-R^3-$ is:

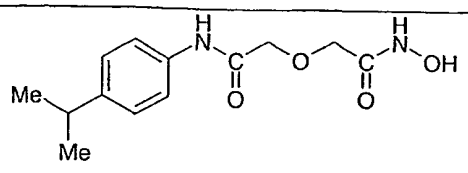


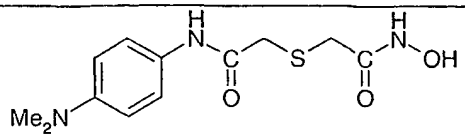
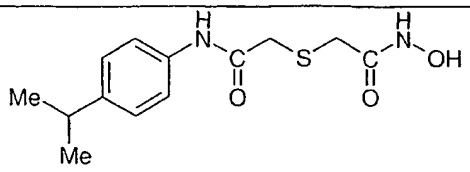
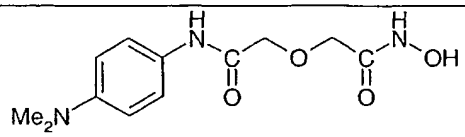
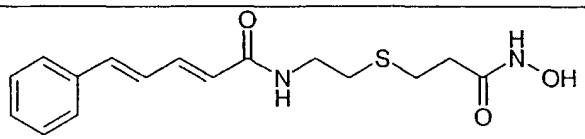
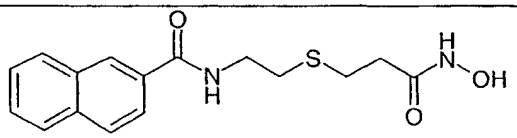
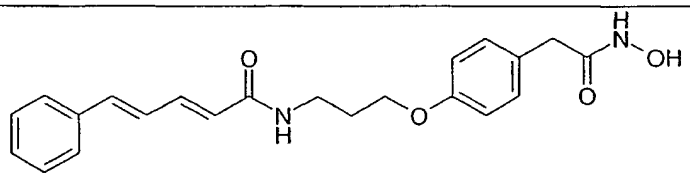
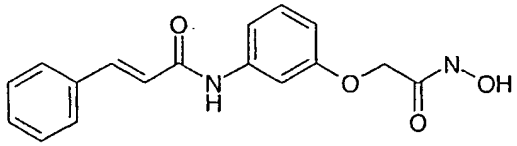
In one preferred embodiment, $-R^2-X-R^3-$ is:



Examples of Specific Embodiments

Some individual embodiments of the present invention include the following compounds.

1		PX083805

2		PX089278
3		PX089279
4		PX089281
5		PX117439
6		PX117440
7		PX117443
8		PX117708

Chemical Terms

The term "carbo," "carbyl," "hydrocarbo," and "hydrocarbyl," as used herein, pertain to compounds and/or groups which have only carbon and hydrogen atoms.

The term "hetero," as used herein, pertains to compounds and/or groups which have at least one heteroatom, for example, multivalent heteroatoms (which are also suitable as ring heteroatoms) such as boron, silicon, nitrogen, phosphorus,

oxygen, and sulfur, and monovalent heteroatoms, such as fluorine, chlorine, bromine, and iodine.

The term "saturated," as used herein, pertains to compounds and/or groups which do not have any carbon-carbon double bonds or carbon-carbon triple bonds.

The term "unsaturated," as used herein, pertains to compounds and/or groups which have at least one carbon-carbon double bond or carbon-carbon triple bond.

The term "aliphatic," as used herein, pertains to compounds and/or groups which are linear or branched, but not cyclic (also known as "acyclic" or "open-chain" groups).

The term "cyclic," as used herein, pertains to compounds and/or groups which have one ring, or two or more rings (e.g., spiro, fused, bridged).

The term "ring," as used herein, pertains to a closed ring of from 3 to 10 covalently linked atoms, more preferably 3 to 8 covalently linked atoms.

The term "aromatic ring," as used herein, pertains to a closed ring of from 3 to 10 covalently linked atoms, more preferably 5 to 8 covalently linked atoms, which ring is aromatic.

The term "heterocyclic ring," as used herein, pertains to a closed ring of from 3 to 10 covalently linked atoms, more preferably 3 to 8 covalently linked atoms, wherein at least one of the ring atoms is a multivalent ring heteroatom, for example, nitrogen, phosphorus, silicon, oxygen, and sulfur, though more commonly nitrogen, oxygen, and sulfur.

The term "alicyclic," as used herein, pertains to compounds and/or groups which have one ring, or two or more rings (e.g., spiro, fused, bridged), wherein said ring(s) are not aromatic.

The term "aromatic," as used herein, pertains to compounds and/or groups which have one ring, or two or more rings (e.g., fused), wherein at least one of said ring(s) is aromatic.

The term "heterocyclic," as used herein, pertains to cyclic compounds and/or groups which have one heterocyclic ring, or two or more heterocyclic rings (e.g., spiro, fused, bridged), wherein said ring(s) may be alicyclic or aromatic.

The term "heteroaromatic," as used herein, pertains to cyclic compounds and/or groups which have one heterocyclic ring, or two or more heterocyclic rings (e.g., fused), wherein said ring(s) is aromatic.

Substituents

The phrase "optionally substituted," as used herein, pertains to a parent group which may be unsubstituted or which may be substituted.

Unless otherwise specified, the term "substituted," as used herein, pertains to a parent group which bears one or more substituents. The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, appended to, or if appropriate, fused to, a parent group. A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known.

In one preferred embodiment, the substituent(s), often referred to herein as R, are independently selected from: halo; hydroxy; ether (e.g., C_{1-7}alkoxy); formyl; acyl (e.g., C_{1-7}alkylacyl , C_{5-20}arylacyl); acylhalide; carboxy; ester; acyloxy; amido; acylamido; thioamido; tetrazolyl; amino; nitro; nitroso; azido; cyano; isocyano; cyanato; isocyanato; thiocyano; isothiocyano; sulfhydryl; thioether (e.g., C_{1-7}alkylthio); sulfonic acid; sulfonate; sulfone; sulfonyloxy; sulfinyloxy; sulfamino; sulfonamino; sulfinamino; sulfamyl; sulfonamido; C_{1-7}alkyl (including, e.g., C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, C_{5-20}aryl-

C_{1-7}alkyl); C_{3-20}heterocyclyl; or C_{5-20}aryl (including, e.g., C_{5-20}carboaryl, C_{5-20}heteroaryl, C_{1-7}alkyl-C_{5-20}aryl and C_{5-20}haloaryl)).

In one preferred embodiment, the substituent(s), often referred to herein as R, are independently selected from:

-F, -Cl, -Br, and -I;

-OH;

-OMe, -OEt, -O(tBu), and -OCH_2Ph;

-SH;

-SMe, -SEt, -S(tBu), and -SCH_2Ph;

-C(=O)H;

-C(=O)Me, -C(=O)Et, -C(=O)(tBu), and -C(=O)Ph;

-C(=O)OH;

-C(=O)OMe, -C(=O)OEt, and -C(=O)O(tBu);

-C(=O)NH_2, -C(=O)NHMe, -C(=O)NMe_2, and -C(=O)NHEt;

-NHC(=O)Me, -NHC(=O)Et, -NHC(=O)Ph, succinimidyl, and maleimidyl;

-NH_2, -NHMe, -NHEt, -NH(iPr), -NH(nPr), -NMe_2, -NEt_2, -$N(iPr)_2$, -$N(nPr)_2$, -$N(nBu)_2$, and -$N(tBu)_2$;

-CN;

-NO_2;

-Me, -Et, -nPr, -iPr, -nBu, -tBu;

-CF_3, -CHF_2, -CH_2F, -CCl_3, -CBr_3, -CH_2CH_2F, -CH_2CHF_2, and -CH_2CF_3;

-OCF_3, -$OCHF_2$, -OCH_2F, -$OCCl_3$, -$OCBr_3$, -OCH_2CH_2F, -OCH_2CHF_2, and -OCH_2CF_3;

-CH_2OH, -CH_2CH_2OH, and -$CH(OH)CH_2OH$;

-CH_2NH_2,-$CH_2CH_2NH_2$, and -$CH_2CH_2NMe_2$; and,

optionally substituted phenyl.

In one preferred embodiment, the substituent(s), often referred to herein as R, are independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -SH, -SMe, -SEt, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -$CONH_2$, -CONHMe, -NH_2, -NMe_2, -NEt_2, -$N(nPr)_2$, -$N(iPr)_2$, -CN, -NO_2, -Me, -Et, -CF_3, -OCF_3, -CH_2OH, -CH_2CH_2OH, -CH_2NH_2, -$CH_2CH_2NH_2$, and -Ph.

In one preferred embodiment, the substituent(s), often referred to herein as R, are independently selected from: hydroxy; ether (e.g., C_{1-7}alkoxy); ester; amido; amino; and, C_{1-7}alkyl (including, e.g., C_{1-7}haloalkyl, C_{1-7}hydroxyalkyl, C_{1-7}carboxyalkyl, C_{1-7}aminoalkyl, C_{5-20}aryl-C_{1-7}alkyl).

In one preferred embodiment, the substituent(s), often referred to herein as R, are independently selected from:

-OH;

-OMe, -OEt, -O(tBu), and -OCH_2Ph;

-C(=O)OMe, -C(=O)OEt, and -C(=O)O(tBu);

-$C(=O)NH_2$, -C(=O)NHMe, -$C(=O)NMe_2$, and -C(=O)NHEt;

-NH_2, -NHMe, -NHEt, -NH(iPr), -NH(nPr), -NMe_2, -NEt_2, -$N(iPr)_2$, -$N(nPr)_2$, -$N(nBu)_2$, and -$N(tBu)_2$;

-Me, -Et, -nPr, -iPr, -nBu, -tBu;

-CF_3, -CHF_2, -CH_2F, -CCl_3, -CBr_3, -CH_2CH_2F, -CH_2CHF_2, and -CH_2CF_3;

-CH_2OH, -CH_2CH_2OH, and -CH(OH)CH_2OH; and,

-CH_2NH_2,-$CH_2CH_2NH_2$, and -$CH_2CH_2NMe_2$.

The substituents are described in more detail below.

C_{1-7}alkyl: The term "C_{1-7}alkyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a C_{1-7}hydrocarbon compound having from 1 to 7 carbon atoms, which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated.

Examples of (unsubstituted) saturated linear C_{1-7}alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, and n-pentyl (amyl).

Examples of (unsubstituted) saturated branched C_{1-7}alkyl groups include, but are not limited to, iso-propyl, iso-butyl, sec-butyl, tert-butyl, and neo-pentyl.

Examples of saturated alicyclic (also carbocyclic) C_{1-7}alkyl groups (also referred to as "C_{3-7}cycloalkyl" groups) include, but are not limited to, unsubstituted groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornane, as well as substituted groups (e.g., groups which comprise such groups), such as methylcyclopropyl, dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl, dimethylcyclohexyl, cyclopropylmethyl and cyclohexylmethyl.

Examples of (unsubstituted) unsaturated C_{1-7}alkyl groups which have one or more carbon-carbon double bonds (also referred to as "C_{2-7}alkenyl" groups) include, but are not limited to, ethenyl (vinyl, -CH=CH_2), 2-propenyl (allyl, -CH-CH=CH_2), isopropenyl (-C(CH_3)=CH_2), butenyl, pentenyl, and hexenyl.

Examples of (unsubstituted) unsaturated C_{1-7}alkyl groups which have one or more carbon-carbon triple bonds (also referred to as "C_{2-7}alkynyl" groups) include, but are not limited to, ethynyl (ethinyl) and 2-propynyl (propargyl).

Examples of unsaturated alicyclic (also carbocyclic) C_{1-7}alkyl groups which have one or more carbon-carbon double bonds (also referred to as "C_{3-7}cycloalkenyl" groups) include, but are not limited to, unsubstituted groups such as cyclopropenyl, cyclobutenyl, cyclopentenyl, and cyclohexenyl, as well as substituted groups (e.g., groups which comprise such groups) such as cyclopropenylmethyl and cyclohexenylmethyl.

Additional examples of substituted C_{3-7}cycloalkyl groups include, but are not limited to, those with one or more other rings fused thereto, for example, those derived from: indene (C_9), indan (2,3-dihydro-1H-indene) (C_9), tetraline (1,2,3,4-tetrahydronaphthalene (C_{10}), adamantane (C_{10}), decalin (decahydronaphthalene) (C_{12}), fluorene (C_{13}), phenalene (C_{13}). For example, 2H-inden-2-yl is a C_5cycloalkyl group with a substituent (phenyl) fused thereto.

C_{3-20}heterocyclyl: The term "C_{3-20}heterocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a

C_{3-20}heterocyclic compound, said compound having one ring, or two or more rings (e.g., spiro, fused, bridged), and having from 3 to 20 ring atoms, of which from 1 to 10 are ring heteroatoms, and wherein at least one of said ring(s) is a heterocyclic ring. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

In this context, the prefixes (e.g., C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6}heterocyclyl," as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C_{3-20}heterocyclyl, C_{3-7}heterocyclyl, C_{5-7}heterocyclyl.

Examples of (non-aromatic) monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N_1: aziridine (C_3), azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);

O_1: oxirane (C_3), oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7);

S_1: thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7);

O_2: dioxolane (C_5), dioxane (C_6), and dioxepane (C_7);

O_3: trioxane (C_6);

N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);

N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);

N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);

N_2O_1: oxadiazine (C_6);

O_1S_1: oxathiole (C_5) and oxathiane (thioxane) (C_6); and,

$N_1O_1S_1$: oxathiazine (C_6).

Examples of substituted (non-aromatic) monocyclic heterocyclyl groups include saccharides, in cyclic form, for example, furanoses (C_5), such as arabinofuranose, lyxofuranose, ribofuranose, and xylofuranse, and pyranoses (C_6), such as allopyranose, altropyranose, glucopyranose, mannopyranose, gulopyranose, idopyranose, galactopyranose, and talopyranose.

Examples of heterocyclyl groups which are also heteroaryl groups are described below with aryl groups.

C_{5-20}aryl: The term "C_{5-20}aryl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of a C_{5-20}aromatic compound, said compound having one ring, or two or more rings (e.g., fused), and having from 5 to 20 ring atoms, and wherein at least one of said ring(s) is an aromatic ring. Preferably, each ring has from 5 to 7 ring atoms.
In this context, the prefixes (e.g., C_{3-20}, C_{5-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms.
For example, the term "C_{5-6}aryl," as used herein, pertains to an aryl group having 5 or 6 ring atoms. Examples of groups of aryl groups include C_{3-20}aryl, C_{5-7}aryl, C_{5-6}aryl.

The ring atoms may be all carbon atoms, as in "carboaryl groups" (e.g., C_{5-20}carboaryl).

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C_6), naphthalene (C_{10}), azulene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), naphthacene (C_{18}), and pyrene (C_{16}).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indene (C_9), isoindene (C_9), and fluorene (C_{13}).

Alternatively, the ring atoms may include one or more heteroatoms, including but not limited to oxygen, nitrogen, and sulfur, as in "heteroaryl groups." In this case, the group may conveniently be referred to as a "C_{5-20}heteroaryl" group, wherein "C_{5-20}" denotes ring atoms, whether carbon atoms or heteroatoms. Preferably, each ring has from 5 to 7 ring atoms, of which from 0 to 4 are ring heteroatoms.

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6);

O_1: furan (oxole) (C_5);

S_1: thiophene (thiole) (C_5);

N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);

N_2O_1: oxadiazole (furazan) (C_5);

N_3O_1: oxatriazole (C_5);

N_1S_1: thiazole (C_5), isothiazole (C_5);

N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);

N_3: triazole (C_5), triazine (C_6); and,

N_4: tetrazole (C_5).

Examples of heterocyclic groups (some of which are also heteroaryl groups) which comprise fused rings, include, but are not limited to:

C_9heterocyclic groups (with 2 fused rings) derived from benzofuran (O_1), isobenzofuran (O_1), indole (N_1), isoindole (N_1), purine (N_4) (e.g., adenine, guanine), benzimidazole (N_2), benzoxazole (N_1O_1), benzisoxazole (N_1O_1), benzodioxole (O_2), benzofurazan (N_2O_1), benzotriazole (N_3), benzothiofuran (S_1), benzothiazole (N_1S_1), benzothiadiazole (N_2S);

C_{10}heterocyclic groups (with 2 fused rings) derived from benzodioxan (O_2), quinoline (N_1), isoquinoline (N_1), benzoxazine (N_1O_1), benzodiazine (N_2), pyridopyridine (N_2), quinoxaline (N_2), quinazoline (N_2);

C_{13}heterocyclic groups (with 3 fused rings) derived from carbazole (N_1), dibenzofuran (O_1), dibenzothiophene (S_1); and,

C_{14}heterocyclic groups (with 3 fused rings) derived from acridine (N_1), xanthene (O_1), phenoxathiin (O_1S_1), phenazine (N_2), phenoxazine (N_1O_1), phenothiazine (N_1S_1), thianthrene (S_2), phenanthridine (N_1), phenanthroline (N_2), phenazine (N_2).

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methypyrrole. Examples of N-substitutents include, but are not limited to C_{1-7}alkyl, C_{3-20}heterocyclyl, C_{5-20}aryl, and acyl groups.

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -N= group may be substituted in the form of an N-oxide, that is, as -N(→O)= (also denoted $-N^+(\rightarrow O^-)=$). For example, quinoline may be substituted to give quinoline N-oxide; pyridine to give pyridine N-oxide; benzofurazan to give benzofurazan N-oxide (also known as benzofuroxan).

Cyclic groups may additionally bear one or more oxo (=O) groups on ring carbon atoms. Monocyclic examples of such groups include, but are not limited to, those derived from:

C_5: cyclopentanone, cyclopentenone, cyclopentadienone;

C_6: cyclohexanone, cyclohexenone, cyclohexadienone;

O_1: furanone (C_5), pyrone (C_6);

N_1: pyrrolidone (pyrrolidinone) (C_5), piperidinone (piperidone) (C_6), piperidinedione (C_6);

N_2: imidazolidone (imidazolidinone) (C_5), pyrazolone (pyrazolinone) (C_5), piperazinone (C_6), piperazinedione (C_6), pyridazinone (C_6), pyrimidinone (C_6) (e.g., cytosine), pyrimidinedione (C_6) (e.g., thymine, uracil), barbituric acid (C_6);

N_1S_1: thiazolone (C_5), isothiazolone (C_5);

N_1O_1: oxazolinone (C_5).

Polycyclic examples of such groups include, but are not limited to, those derived from:

C_9: indenedione;

N_1: oxindole (C_9);

O_1: benzopyrone (e.g., coumarin, isocoumarin, chromone) (C_{10});

N_1O_1: benzoxazolinone (C_9), benzoxazolinone (C_{10});

N_2: quinazolinedione (C_{10});

N_4: purinone (C_9) (e.g., guanine).

Still more examples of cyclic groups which bear one or more oxo (=O) groups on ring carbon atoms include, but are not limited to, those derived from:

cyclic anhydrides (-C(=O)-O-C(=O)- in a ring), including but not limited to maleic anhydride (C_5), succinic anhydride (C_5), and glutaric anhydride (C_6);

cyclic carbonates (-O-C(=O)-O- in a ring), such as ethylene carbonate (C_5) and 1,2-propylene carbonate (C_5);

imides (-C(=O)-NR-C(=O)- in a ring), including but not limited to, succinimide (C_5), maleimide (C_5), phthalimide, and glutarimide (C_6);

lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to, β-propiolactone, γ-butyrolactone, δ-valerolactone (2-piperidone), and ε-caprolactone;

lactams (cyclic amides, -NR-C(=O)- in a ring), including, but not limited to, β-propiolactam (C_4), γ-butyrolactam (2-pyrrolidone) (C_5), δ-valerolactam (C_6), and ε-caprolactam (C_7);

cyclic carbamates (-O-C(=O)-NR- in a ring), such as 2-oxazolidone (C_5);

cyclic ureas (-NR-C(=O)-NR- in a ring), such as 2-imidazolidone (C_5) and pyrimidine-2,4-dione (e.g., thymine, uracil) (C_6).

The above C_{1-7}alkyl, C_{3-20}heterocyclyl, and C_{5-20}aryl groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below.

Hydrogen: -H. Note that if the substituent at a particular position is hydrogen, it may be convenient to refer to the compound as being "unsubstituted" at that position.

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C_{1-7}alkyl group (also referred to as a C_{1-7}alkoxy group, discussed below), a C_{3-20}heterocyclyl group (also referred to as a C_{3-20}hetercyclyloxy group), or a C_{5-20}aryl group (also referred to as a C_{5-20}aryloxy group), preferably a C_{1-7}alkyl group.

C_{1-7}alkoxy: -OR, wherein R is a C_{1-7}alkyl group. Examples of C_{1-7}alkoxy groups include, but are not limited to, $-OCH_3$ (methoxy), $-OCH_2CH_3$ (ethoxy) and $-OC(CH_3)_3$ (tert-butoxy).

Oxo (keto, -one): =O. Examples of cyclic compounds and/or groups having, as a substituent, an oxo group (=O) include, but are not limited to, carbocyclics such as cyclopentanone and cyclohexanone; heterocyclics, such as pyrone, pyrrolidone, pyrazolone, pyrazolinone, piperidone, piperidinedione, piperazinedione, and imidazolidone; cyclic anhydrides, including but not limited to maleic anhydride and

succinic anhydride; cyclic carbonates, such as propylene carbonate; imides, including but not limited to, succinimide and maleimide; lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to, β-propiolactone, γ-butyrolactone, δ-valerolactone, and ε-caprolactone; and lactams (cyclic amides, -NH-C(=O)- in a ring), including, but not limited to, β-propiolactam, γ-butyrolactam, δ-valerolactam, and ε-caprolactam.

Imino (imine): =NR, wherein R is an imino substituent, for example, hydrogen, C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of imino groups include, but are not limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H.

Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for example, a C_{1-7}alkyl group (also referred to as C_{1-7}alkylacyl or C_{1-7}alkanoyl), a C_{3-20}heterocyclyl group (also referred to as C_{3-20}heterocyclylacyl), or a C_{5-20}aryl group (also referred to as C_{5-20}arylacyl), preferably a C_{1-7}alkyl group. Examples of acyl groups include, but are not limited to, -C(=O)CH_3 (acetyl), -C(=O)CH_2CH_3 (propionyl), -C(=O)$C(CH_3)_3$ (butyryl), and -C(=O)Ph (benzoyl, phenone).

Acylhalide (haloformyl, halocarbonyl): -C(=O)X, wherein X is -F, -Cl, -Br, or -I, preferably -Cl, -Br, or -I.

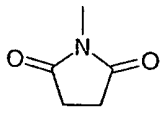
Carboxy (carboxylic acid): -COOH.

Ester (carboxylate, carboxylic acid ester, oxycarbonyl): -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of ester groups include, but are not limited to, -C(=O)OCH_3, -C(=O)OCH_2CH_3, -C(=O)$OC(CH_3)_3$, and -C(=O)OPh.

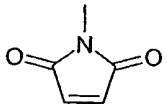
Acyloxy (reverse ester): -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of acyloxy groups include, but are not limited to, -OC(=O)CH_3 (acetoxy), -OC(=O)CH_2CH_3, -OC(=O)$C(CH_3)_3$, -OC(=O)Ph, and -OC(=O)CH_2Ph.

Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): -C(=O)NR^1R^2, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, -C(=O)NH_2, -C(=O)$NHCH_3$, -C(=O)$NH(CH_3)_2$, -C(=O)$NHCH_2CH_3$, and -C(=O)$N(CH_2CH_3)_2$, as well as amido groups in which R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

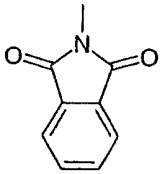
Acylamido (acylamino): -NR^1C(=O)R^2, wherein R^1 is an amide substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group, and R^2 is an acyl substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of acylamido groups include, but are not limited to, -NHC(=O)CH_3 , -NHC(=O)CH_2CH_3, and -NHC(=O)Ph. R^1 and R^2 may together form a cyclic structure, as in, for example, for example, succinimidyl, maleimidyl, and phthalimidyl:



succinimidyl



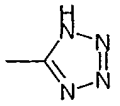
maleimidyl



phthalimidyl

Thioamido (thiocarbamyl): -C(=S)NR^1R^2, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, -C(=S)NH_2, -C(=S)$NHCH_3$, -C(=S)$NH(CH_3)_2$, and -C(=S)$NHCH_2CH_3$.

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7}alkyl group (also referred to as C_{1-7}alkylamino or di-C_{1-7}alkylamino), a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably H or a C_{1-7}alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHCH(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and -NHPh. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, piperidino, piperazino, morpholino, and thiomorpholino.

Nitro: $-NO_2$.

Nitroso: -NO.

Azido: $-N_3$.

Cyano (nitrile, carbonitrile): -CN.

Isocyano: -NC.

Cyanato: -OCN.

Isocyanato: -NCO.

Thiocyano (thiocyanato): -SCN.

Isothiocyano (isothiocyanato): -NCS.

Sulfhydryl (thiol, mercapto): -SH.

Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a C_{1-7}alkyl group (also referred to as a C_{1-7}alkylthio group), a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of C_{1-7}alkylthio groups include, but are not limited to, $-SCH_3$ and $-SCH_2CH_3$.

Sulfonic acid (sulfo): $-S(=O)_2OH$.

Sulfonate (sulfonic acid ester): $-S(=O)_2OR$, wherein R is a sulfonate substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonate groups include, but are not limited to, $-S(=O)_2OCH_3$ and $-S(=O)_2OCH_2CH_3$.

Sulfone (sulfonyl): $-S(=O)_2R$, wherein R is a sulfone substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfone groups include, but are not limited to, $-S(=O)_2CH_3$ (methanesulfonyl, mesyl), $-S(=O)_2CF_3$, $-S(=O)_2CH_2CH_3$, and 4-methylphenylsulfonyl (tosyl).

Sulfonyloxy: $-OS(=O)_2R$, wherein R is a sulfonyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonyloxy groups include, but are not limited to, $-OS(=O)_2CH_3$ and $-OS(=O)_2CH_2CH_3$.

Sulfinyloxy: $-OS(=O)R$, wherein R is a sulfinyloxy substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinyloxy groups include, but are not limited to, $-OS(=O)CH_3$ and $-OS(=O)CH_2CH_3$.

Sulfamino: $-NR^1S(=O)_2OH$, wherein R^1 is an amino substituent, as defined for amino groups. Examples of sulfamino groups include, but are not limited to, $-NHS(=O)_2OH$ and $-N(CH_3)S(=O)_2OH$.

Sulfonamino: $-NR^1S(=O)_2R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonamino groups include, but are not limited to, $-NHS(=O)_2CH_3$ and $-N(CH_3)S(=O)_2C_6H_5$.

Sulfinamino: $-NR^1S(=O)R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinamino groups include, but are not limited to, $-NHS(=O)CH_3$ and $-N(CH_3)S(=O)C_6H_5$.

Sulfamyl: $-S(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-S(=O)NH_2$, $-S(=O)NH(CH_3)$, $-S(=O)N(CH_3)_2$, $-S(=O)NH(CH_2CH_3)$, $-S(=O)N(CH_2CH_3)_2$, and $-S(=O)NHPh$.

Sulfonamido: $-S(=O)_2NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to, $-S(=O)_2NH_2$, $-S(=O)_2NH(CH_3)$, $-S(=O)_2N(CH_3)_2$, $-S(=O)_2NH(CH_2CH_3)$, $-S(=O)_2N(CH_2CH_3)_2$, and $-S(=O)_2NHPh$.

As mentioned above, a C_{1-7}alkyl group may be substituted with, for example, hydroxy (also referred to as a C_{1-7}hydroxyalkyl group), C_{1-7}alkoxy (also referred to as a C_{1-7}alkoxyalkyl group), amino (also referred to as a C_{1-7}aminoalkyl group), halo (also referred to as a C_{1-7}haloalkyl group), carboxy (also referred to as a C_{1-7}carboxyalkyl group), and C_{5-20}aryl (also referred to as a C_{5-20}aryl-C_{1-7}alkyl group).

Similarly, a C_{5-20}aryl group may be substituted with, for example, hydroxy (also referred to as a C_{5-20}hydroxyaryl group), halo (also referred to as a C_{5-20}haloaryl group), amino (also referred to as a C_{5-20}aminoaryl group, e.g., as in aniline), C_{1-7}alkyl (also referred to as a C_{1-7}alkyl-C_{5-20}aryl group, e.g., as in toluene), and C_{1-7}alkoxy (also referred to as a C_{1-7}alkoxy-C_{5-20}aryl group, e.g., as in anisole).

These and other specific examples of such substituted groups are also discussed below.

C_{1-7}haloalkyl group: The term "C_{1-7}haloalkyl group," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a halogen atom (e.g., F, Cl, Br, I). If more than one hydrogen atom has been replaced with a halogen atom, the halogen atoms may independently be the same or different. Every hydrogen atom may be replaced with a halogen atom, in which case the group may conveniently be referred to as a C_{1-7}perhaloalkyl group." Examples of C_{1-7}haloalkyl groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CBr_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, and $-CH_2CF_3$.

C_{1-7}hydroxyalkyl: The term "C_{1-7}hydroxyalkyl group," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom has been replaced with a hydroxy group. Examples of C_{1-7}hydroxyalkyl groups include, but are not limited to, $-CH_2OH$,$-CH_2CH_2OH$, and $-CH(OH)CH_2OH$.

C_{1-7}carboxyalkyl: The term "C_{1-7}carboxyalkyl group," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom has been replaced with a carboxy group. Examples of C_{1-7}carboxyalkyl groups include, but are not limited to, $-CH_2COOH$ and $-CH_2CH_2COOH$.

C_{1-7}aminoalkyl: The term "C_{1-7}aminoalkyl group," as used herein, pertains to a C_{1-7}alkyl group in which at least one hydrogen atom has been replaced with an amino group. Examples of C_{1-7}aminoalkyl groups include, but are not limited to, $-CH_2NH_2$,$-CH_2CH_2NH_2$, and $-CH_2CH_2N(CH_3)_2$.

C_{1-7}alkyl-C_{5-20}aryl: The term "C_{1-7}alkyl-C_{5-20}aryl," as used herein, describes certain C_{5-20}aryl groups which have been substituted with a C_{1-7}alkyl group. Examples of such groups include, but are not limited to, tolyl (as in toluene), xylyl (as in xylene), mesityl (as in mesitylene), styryl (as in styrene), and cumenyl (as in cumene).

C_{5-20}aryl-C_{1-7}alkyl: The term "C_{5-20}aryl-C_{1-7}alkyl," as used herein, describers certain C_{1-7}alkyl groups which have been substituted with a C_{5-20}aryl group. Examples of such groups include, but are not limited to, benzyl (phenylmethyl), tolylmethyl, phenylethyl, and triphenylmethyl (trityl).

C_{5-20}haloaryl: The term "C_{5-20}haloaryl," as used herein, describes certain C_{5-20}aryl groups which have been substituted with one or more halo groups. Examples of such groups include, but are not limited to, halophenyl (e.g., fluorophenyl, chlorophenyl, bromophenyl, or iodophenyl, whether ortho-, meta-, or para-substituted), dihalophenyl, trihalophenyl, tetrahalophenyl, and pentahalophenyl.

Bidentate Substituents

Some substituents are bidentate, that is, have two points for covalent attachment. For example, a bidentate group may be covalently bound to two different atoms on two different groups, thereby acting as a linker therebetween. Alternatively, a bidentate group may be covalently bound to two different atoms on the same group, thereby forming, together with the two atoms to which it is attached (and any intervening atoms, if present) a cyclic or ring structure. In this way, the bidentate substituent may give rise to a heterocyclic group/compound and/or an aromatic group/compound. Typically, the ring has from 3 to 8 ring atoms, which ring atoms are carbon or divalent heteroatoms (e.g., boron, silicon, nitrogen, phosphorus, oxygen, and sulfur, typically nitrogen, oxygen, and sulfur), and wherein the bonds between said ring atoms are single or double bonds, as permitted by the valencies of the ring atoms. Typically, the bidentate group is covalently bound to vicinal atoms, that is, adjacent atoms, in the parent group.

C_{1-7}alkylene: The term "C_{1-7}alkylene," as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms, either both from the same carbon atom, or one from each of two different carbon atoms, of a C_{1-7}hydrocarbon compound having from 1 to 7 carbon atoms, which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated.

Examples of linear saturated C_{1-7}alkylene groups include, but are not limited to, -$(CH_2)_n$- where n is an integer from 1 to 7, for example, -CH_2- (methylene), -CH_2CH_2- (ethylene), -$CH_2CH_2CH_2$- (propylene), and -$CH_2CH_2CH_2CH_2$- (butylene).

Examples of branched saturated C_{1-7}alkylene groups include, but are not limited to, -$CH(CH_3)$-, -$CH(CH_3)CH_2$-, -$CH(CH_3)CH_2CH_2$-, -$CH(CH_3)CH_2CH_2CH_2$-, -$CH_2CH(CH_3)CH_2$-, -$CH_2CH(CH_3)CH_2CH_2$-, -$CH(CH_2CH_3)$-, -$CH(CH_2CH_3)CH_2$-, and -$CH_2CH(CH_2CH_3)CH_2$-.

Examples of linear partially unsaturated C_{1-7}alkylene groups include, but are not limited to, -CH=CH- (vinylene), -CH=CH-CH_2-, -CH=CH-CH_2-CH_2-, -CH=CH-CH_2-CH_2-CH_2-, -CH=CH-CH=CH-, -CH=CH-CH=CH-CH_2-, -CH=CH-CH=CH-CH_2-CH_2-, -CH=CH-CH_2-CH=CH-, and -CH=CH-CH_2-CH_2-CH=CH-.

Examples of branched partially unsaturated C_{1-7}alkylene groups include, but are not limited to, -$C(CH_3)$=CH-, -$C(CH_3)$=CH-CH_2-, and -CH=CH-$CH(CH_3)$-.

Examples of alicyclic saturated C_{1-7}alkylene groups include, but are not limited to, cyclopentylene (e.g., cyclopent-1,3-ylene), and cyclohexylene (e.g., cyclohex-1,4-ylene).

Examples of alicyclic partially unsaturated C_{1-7}alkylene groups include, but are not limited to, cyclopentenylene (e.g., 4-cyclopenten-1,3-ylene), cyclohexenylene (e.g., 2-cyclohexen-1,4-ylene, 3-cyclohexen-1,2-ylene, 2,5-cyclohexadien-1,4-ylene).

C_{5-20}arylene: The term "C_{5-20}arylene," as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms, one from each of two different ring atoms of a C_{5-20}aromatic compound, said compound having one ring, or two or more rings (e.g., fused), and having from 5 to 20 ring atoms, and wherein at least one of said ring(s) is an aromatic ring. Preferably, each ring has from 5 to 7 ring atoms.

The ring atoms may be all carbon atoms, as in "carboarylene groups," in which case the group may conveniently be referred to as a "C_{5-20}carboarylene" group.

Alternatively, the ring atoms may include one or more heteroatoms, including but not limited to oxygen, nitrogen, and sulfur, as in "heteroarylene groups." In this case, the group may conveniently be referred to as a "C_{5-20}heteroarylene" group, wherein "C_{5-20}" denotes ring atoms, whether carbon atoms or heteroatoms. Preferably, each ring has from 5 to 7 ring atoms, of which from 0 to 4 are ring heteroatoms.

Examples of C_{5-20}arylene groups which do not have ring heteroatoms (i.e., C_{5-20}carboarylene groups) include, but are not limited to, those derived from benzene (i.e., phenyl) (C_6), naphthalene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), and pyrene (C_{16}).

Examples of C_{5-20}heteroarylene groups include, but are not limited to, C_5heteroarylene groups derived from furan (oxole), thiophene (thiole), pyrrole (azole), imidazole (1,3-diazole), pyrazole (1,2-diazole), triazole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, and oxatriazole; and C_6heteroarylene groups derived from isoxazine, pyridine (azine), pyridazine (1,2-diazine), pyrimidine (1,3-diazine; e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine), triazine, tetrazole, and oxadiazole (furazan).

C_{5-20}Arylene-C_{1-7}alkylene: The term "C_{5-20}arylene-C_{1-7}alkylene," as used herein, pertains to a bidentate moiety comprising a C_{5-20}arylene moiety, -Arylene-, linked to a C_{1-7}alkylene moiety, -Alkylene-, that is, -Arylene-Alkylene-.

Examples of C_{5-20}arylene-C_{1-7}alkylene groups include, but are not limited to, phenylene-methylene, phenylene-ethylene, phenylene-propylene, and phenylene-ethenylene (also known as phenylene-vinylene).

C_{5-20}Alkylene-C_{1-7}arylene: The term "C_{5-20}alkylene-C_{1-7}arylene," as used herein, pertains to a bidentate moiety comprising a C_{5-20}alkylene moiety, -Alkylene-, linked to a C_{1-7}arylene moiety, -Arylene-, that is, -Alkylene-Arylene-.

Examples of C_{5-20}alkylene-C_{1-7}arylene groups include, but are not limited to, methylene-phenylene, ethylene-phenylene, propylene-phenylene, and ethenylene-phenylene (also known as vinylene-phenylene).

Included in the above are the well known ionic, salt, solvate (e.g., hydrate), and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes carboxylate ($-COO^-$). Similarly, a reference to an amino group includes a salt, for example, a hydrochloride salt, of the amino group. A reference to a hydroxyl group also includes conventional protected forms of a hydroxyl group. Similarly, a reference to an amino group also includes conventional protected forms of an amino group.

Acronyms

For convenience, many chemical moieties are represented herein using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

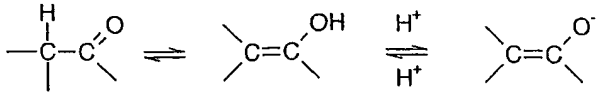
For convenience, many chemical compounds are represented herein using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), acetic acid (AcOH), dichloromethane (methylene chloride, DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF), and tetrahydrofuran (THF).

Isomers, Salts, Hydrates, Protected Forms, and Prodrugs

A certain compound may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_{1-7}alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including racemic and other mixtures thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein in a known manner.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate (e.g., hydrate), protected forms, and prodrugs thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na+ and K+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{+3}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous. Examples of suitable organic anions include, but are not limited to, anions from the following organic acids: acetic, propionic, succinic, gycolic, stearic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetyoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethanesulfonic, ethane disulfonic, oxalic, isethionic, and valeric.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form," as used herein, pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions, that is, are in the form of a protected or protecting group (also known as a masked or masking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts, Wiley, 1991), and Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl

(diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal or ketal, respectively, in which the carbonyl group (>C=O) is converted to a diether (>$C(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulfonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O•).

For example, a carboxylic acid group may be protected as an ester or an amide, for example, as: a benzyl ester; a t-butyl ester; a methyl ester; or a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-$CH_2NHC(=O)CH_3$).

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound which, when metabolised, yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolysis, the ester group is cleaved to yield the active drug. Also, some prodrugs are

activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound. For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Synthesis

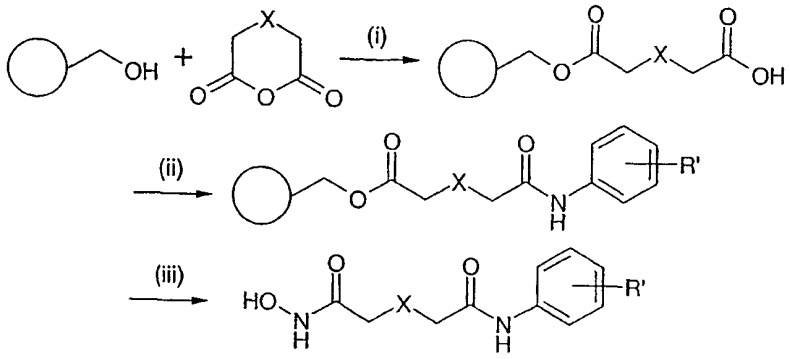
Several methods for the chemical synthesis of compounds of the present invention are described herein. These methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional compounds within the scope of the present invention.

The compounds of the present invention may be prepared, for example, by the methods described herein, or by adapting these or other well known methods in well known ways.

In one method, a suitable resin with pendant hydroxy groups is reacted with a suitable carboxylic acid or anhydride, to form a pendant group which is linked to the solid support via an ester group, and which has a terminal carboxylic acid group. The terminal carboxylic acid group is then reacted with a suitable aryl amine (e.g., NH_2R), for example, an aniline, to give a terminal aryl amide. The resulting compound is then cleaved from the resin using hydroxylamine to give the desired carbamic acid.

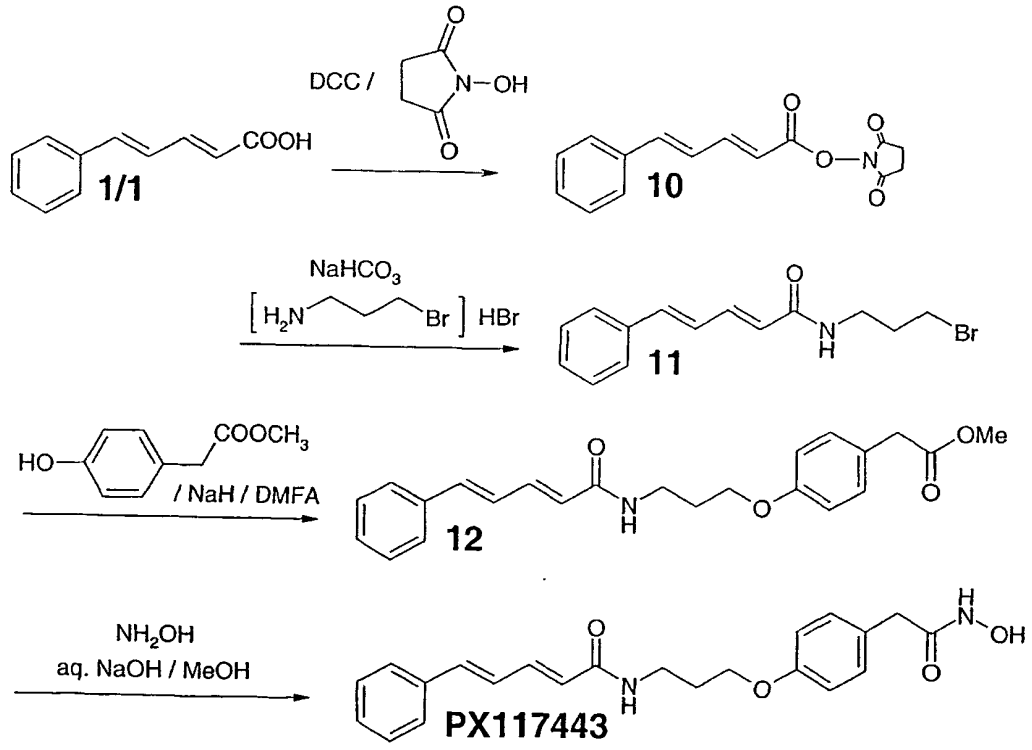
One example of this approach is illustrated below, wherein the resin is ArgoGelJ-OH resin, X is -O- or -S-, and the reaction conditions are as follows: (i) DCM/pyridine (1:1, v/v), DMAP, room temperature, 16 hours; (ii) NH_2R, HOBT, TBTU, DIPEA, NMP, room temperature, 16 hours; and (iii) 50% NH_2OH, dioxane, room temperature, 48 hours.

Scheme 1

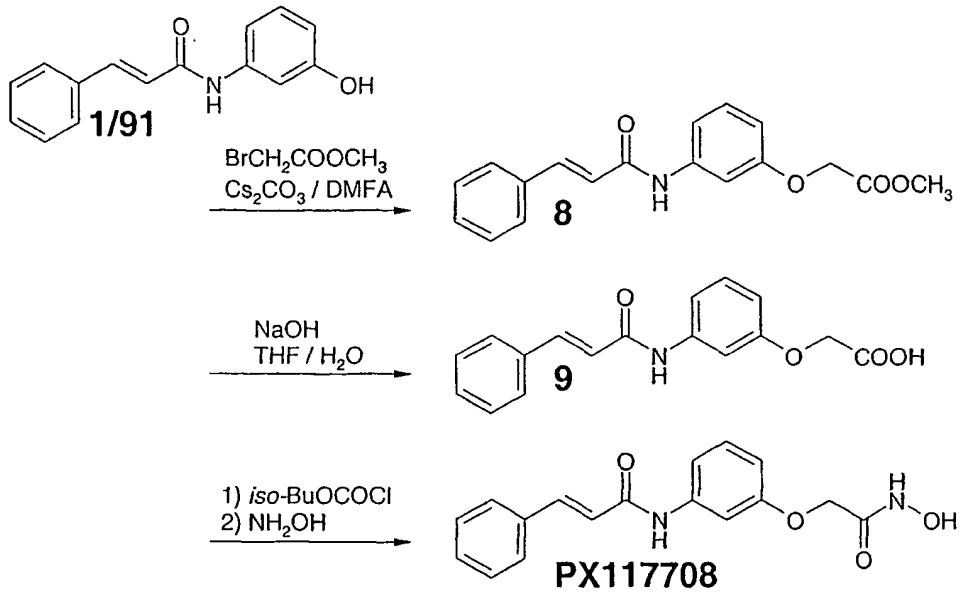


Additional methods for the synthesis of compounds of the present invention are illustrated below and are exemplified in the examples below.

Scheme 2



Scheme 3



Uses

The present invention provides active compounds which are capable of inhibiting HDAC (for example, inhibiting HDAC activity, inhibiting formation of HDAC complexes, inhibiting activity of HDAC complexes), as well as methods of inhibiting HDAC activity, comprising contacting a cell with an effective amount of an active compound, whether *in vitro* or *in vivo*.

The term "active," as used herein, pertains to compounds which are capable of inhibiting HDAC activity, and specifically includes both compounds with intrinsic activity (drugs) as well as prodrugs of such compounds, which prodrugs may themselves exhibit little or no intrinsic activity.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound is active, that is, capable of inhibiting HDAC activity. For example, assays which may conveniently be used to assess the inhibition offered by a particular compound are described in the examples below.

For example, a sample of cells (e.g., from a tumour) may be grown *in vitro* and a candidate compound brought into contact with the cells, and the effect of the compound on those cells observed. As examples of "effect," the morphological status of the cells may be determined (e.g., alive or dead), or the expression levels of genes regulated by HDAC. Where the candidate compound is found to exert an influence on the cells, this may be used as a prognostic or diagnostic marker of the efficacy of the compound in methods of treating a patient carrying cells of the same type (e.g., the tumour or a tumour of the same cellular type).

In one aspect, the present invention provides antiproliferative agents. The term "antiproliferative agent" as used herein, pertains to a compound which treats a proliferative condition (i.e., a compound which is useful in the treatment of a proliferative condition).

The terms "cell proliferation," "proliferative condition," "proliferative disorder," and "proliferative disease," are used interchangeably herein and pertain to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether *in vitro* or *in vivo*. Examples of proliferative conditions include, but are not limited to, pre-malignant and malignant cellular proliferation, including but not limited to, malignant neoplasms and tumours, cancers, leukemias, psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), and atherosclerosis. Any type of cell may be treated, including but not limited to, lung, colon, breast, ovarian, prostate, liver, pancreas, brain, and skin.

Antiproliferative compounds of the present invention have application in the treatment of cancer, and so the present invention further provides anticancer agents. The term "anticancer agent" as used herein, pertains to a compound which treats a cancer (i.e., a compound which is useful in the treatment of a cancer). The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the regulation of cell proliferation, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of invasion (the spread of

tumour cells into neighbouring normal structures), or the promotion of apoptosis (programmed cell death).

The compounds of the present invention may also be used in the treatment of conditions which are known to be mediated by HDAC, or which are known to be treated by HDAC inhibitors (such as, e.g., trichostatin A). Examples of such conditions include, but are not limited to, the following:

Cancer (see, e.g., Vigushin et al., 2001).

Psoriasis (see, e.g., Iavarone et al., 1999).

Fibroproliferative disorders (e.g., liver fibrosis) (see, e.g., Niki et al., 1999; Corneil et al., 1998).

Smooth muscle proliferative disorder (e.g., atherosclerosis, restenosis) (see, e.g., Kimura et al., 1994).

Neurodegenative diseases (e.g., Alzheimer's, Parkinson's, Huntington's chorea, amyotropic lateral sclerosis, spino-cerebellar degeneration) (see, e.g., Kuusisto et al., 2001).

Inflammatory disease (e.g., osteoarthritis, rheumatoid arthritis) (see, e.g., Dangond et al., 1998; Takahashi et al., 1996).

Diseases involving angiogenesis (e.g., cancer, rheumatoid arthritis, psoriasis, diabetic retinopathy) (see, e.g., Kim et al., 2001).

Haematopoietic disorders (e.g., anaemia, sickle cell anaemia, thalassaeimia) (see, e.g., McCaffrey et al., 1997).

Fungal infection (see, e.g., Bernstein et al., 2000; Tsuji et al., 1976).

Parasitic infection (e.g., malaria, trypanosomiasis, helminthiasis, protozoal infections (see, e.g., Andrews et al., 2000).

Bacterial infection (see, e.g., Onishi et al., 1996).

Viral infection (see, e.g., Chang et al., 2000).

Conditions treatable by immune modulation (e.g., multiple sclerosis, autoimmune diabetes, lupus, atopic dermatitis, allergies, asthma, allergic rhinitis, inflammatory bowel disease; and for improving grafting of transplants) (see, e.g., Dangond et al., 1998; Takahashi et al., 1996).

The invention further provides active compounds for use in a method of treatment of the human or animal body. Such a method may comprise administering to such a subject a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure is also included.

The term "therapeutically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio.

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. Examples of treatments and therapies include, but are not limited

to, chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; and gene therapy.

The invention further provides the use of an active compound for the manufacture of a medicament, for example, for the treatment of a proliferative condition, as discussed above.

The invention further provides the use of an active compound for the manufacture of a medicament, for example, for the treatment of conditions which are known to be mediated by HDAC, or which are known to be treated by HDAC inhibitors (such as, e.g., trichostatin A), as discussed above.

The invention further provides a method for inhibiting HDAC in a cell comprising said cell with an effective amount of an active compound.

The invention further provides a method of treatment of the human or animal body, the method comprising administering to a subject in need of treatment a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

Active compounds may also be used, as described above, in combination therapies, that is, in conjunction with other agents, for example, cytotoxic agents.

Active compounds may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

Active compounds may also be used as a standard, for example, in an assay, in order to identify other active compounds, other antiproliferative agents, etc.

The compounds of the present invention may also be used in methods of improving protein production by cultured cells (see, e.g., Furukawa et al., 1998).

Routes of Administration

The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g, by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

The Subject

The subject may be a prokaryote (e.g., bacteria) or a eukaryote (e.g., protoctista, fungi, plants, animals).

The subject may be a protoctista, an alga, or a protozoan.

The subject may be a plant, an angiosperm, a dicotyledon, a monocotyledon, a gymnosperm, a conifer, a ginkgo, a cycad, a fern, a horsetail, a clubmoss, a liverwort, or a moss.

The subject may be an animal.

The subject may be a chordate, an invertebrate, an echinoderm (e.g., starfish, sea urchins, brittlestars), an arthropod, an annelid (segmented worms) (e.g., earthworms, lugworms, leeches), a mollusk (cephalopods (e.g., squids, octopi), pelecypods (e.g., oysters, mussels, clams), gastropods (e.g., snails, slugs)), a nematode (round worms), a platyhelminthes (flatworms) (e.g., planarians, flukes, tapeworms), a cnidaria (e.g., jelly fish, sea anemones, corals), or a porifera (e.g., sponges).

The subject may be an arthropod, an insect (e.g., beetles, butterflies, moths), a chilopoda (centipedes), a diplopoda (millipedes), a crustacean (e.g., shrimps, crabs, lobsters), or an arachnid (e.g., spiders, scorpions, mites).

The subject may be a chordate, a vertebrate, a mammal, a bird, a reptile (e.g., snakes, lizards, crocodiles), an amphibian (e.g., frogs, toads), a bony fish (e.g., salmon, plaice, eel, lungfish), a cartilaginous fish (e.g., sharks, rays), or a jawless fish (e.g., lampreys, hagfish).

The subject may be a mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a monotreme (e.g., duckbilled platypus), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject may be any of its forms of development, for example, a spore, a seed, an egg, a larva, a pupa, or a foetus.

In one preferred embodiment, the subject is a human.

Formulations

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g., formulation) comprising at least one active ingredient, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials well known to those skilled in the art and optionally other therapeutic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active ingredient, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials, as described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of a subject (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations may be in the form of liquids, solutions, suspensions, emulsions, tablets, losenges, granules, powders, capsules, cachets, pills, ampoules,

suppositories, pessaries, ointments, gels, pastes, creams, sprays, foams, lotions, oils, boluses, electuaries, or aerosols.

Formulations suitable for oral administration (e.g., by ingestion) may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an electuary; or as a paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (*e.g.*, povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration (e.g., transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, paste, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active ingredients and optionally one or more excipients or diluents.

Formulations suitable for topical administration in the mouth include losenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration as, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active ingredient.

Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active ingredient may optionally be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

When formulated as a topical emulsion, the oily phase may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulfate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g., by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active ingredient in the solution is from about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freese-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Formulations may be in the form of liposomes or other microparticulate systems which are designed to target the active compound to blood components or one or more organs.

Dosage

It will be appreciated that appropriate dosages of the active compounds, and compositions comprising the active compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present invention. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of

administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect.

Administration *in vivo* can be effected in one dose, continuously or intermittently throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

In general, a suitable dose of the active compound is in the range of about 0.1 to about 250 mg per kilogram body weight of the subject per day. Where the active ingredient is a salt, an ester, prodrug, or the like, the amount administered is calculated on the basis the parent compound and so the actual weight to be used is increased proportionately.

Kits

One aspect of the invention pertains to a kit comprising (a) the active ingredient, preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the active compound.

The written instructions may also include a list of indications for which the active ingredient is a suitable treatment.

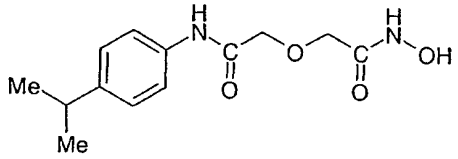
EXAMPLES

The following are examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

Example 1

N-Hydroxy-2-(4-Isopropyl-phenylcarbamoyl)-methoxy)-acetamide

(**PX083805**)



ArgoGelJ-OH resin (500 mg, 0.245 mmol) was placed in a reaction vessel and was swollen by the addition of dichloromethane / pyridine (1:1, v/v) (2 ml). A solution of diglycolic anhydride (142 m, 1.225 mmol), and 4-(dimethylamino)pyridine (DMAP) (15 mg, 0.1225 mmol) in dichloromethane / pyridine (1:1, v/v) (2 ml) was added and the resultant suspension was agitated at ambient temperature for sixteen hours. The resin was filtered and was washed with 1-methylpyrrolidine (5 ml) and alternately with methanol (4 x 5 ml) and dichloromethane (4 x 5 ml). The resin was dried and a sample was analysed by IR spectroscopy (IR(resin/cm^{-1}): 1736 (ester)).

The resin (500 mg, 0.245 mmol) obtained from the first step was placed in a reaction vessel and was swollen by the addition of 1-methylpyrrolidine (2 ml). A solution of 4-isopropylaniline (133 mg, 0.98 mmol), 1-hydroxybenzotriazole (HOBT) (66 mg, 0.49 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-teramethyluronium tetrafluoroborate (TBTU) (315 mg, 0.98 mmol), *N,N*-diisopropylethylamine (DIPEA) (192 µl, 2.205 mmol) in 1-methylpyrrolidine (2 ml) was added and the resultant suspension was agitated at ambient temperature for sixteen hours. The resin was filtered and was washed with 1-methylpyrrolidine (5 ml) and alternately with methanol (4 x 5 ml) and dichloromethane (4 x 5 ml). The resin was dried and a sample was analysed by IR spectroscopy (IR(resin/cm^{-1}) 1692 (amide) and 1754 (ester)).

The resin (500 mg, 0.245 mmol) obtained from the second step was placed in a reaction vessel and was swollen by the addition of 1,4-dioxane (4 ml). A 50% wt solution of hydroxylamine in water (0.4 ml, 6.125 mmol) was added and the resultant suspension was agitated at ambient temperature for forty-eight hours.

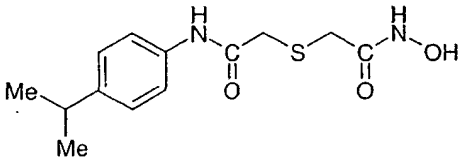
The resin was filtered and washed with a mixture of dioxane and water (1:1, v/v) (5 ml). The filtrates were combined and the solvent was removed under reduced pressure.

The crude product obtained was purified by preparative hplc using a 150 x 21.2 mm 5 µm Hypersil7 Elite C_{18} column eluting with 30% ACN/70% H_2O + 0.2% TFA. The flow rate was 20 $mlmin^{-1}$ and the detector was set at 254 nm. The fractions that contained the desired product were concentrated under reduced pressure and the resultant residue was lyophilised from a mixture of dioxane and water to afford the desired product as a white solid (5.4 mg, 8 %), t_R 3.34 (254 nm, 1.5 $mlmin^{-1}$, 30% ACN/70% H_2O + 0.2% TFA), *m/z* [ES] 265 $[M - H]^-$.

Example 2

N-Hydroxy-2-(4-Isopropyl-phenylcarbamoyl)-methylsulfanyl)-acetamide

(PX089279)



ArgoGelJ-OH resin (500 mg, 0.245 mmol) was placed in a reaction vessel and was swollen by the addition of dichloromethane / pyridine (1:1, v/v) (2 ml). A solution of thiodiglycolic anhydride (162 mg. 1.225 mmol), and 4-(dimethylamino)pyridine (DMAP) (15 mg, 0.1225 mmol) in dichloromethane / pyridine (1:1, v/v) (2 ml) was added and the resultant suspension was agitated at ambient temperature for sixteen hours. The resin was filtered and was washed with 1-methylpyrrolidine (5 ml) and alternately with methanol (4 x 5 ml) and dichloromethane (4 x 5 ml). The resin was dried and a sample was analysed by IR spectroscopy (IR(resin/cm^{-1}) 1732 (ester)).

The resin (500 mg, 0.245 mmol) obtained from the first step was placed in a reaction vessel and was swollen by the addition of 1-methylpyrrolidine (2 ml). A solution of 4-isopropylaniline (133 mg, 0.98 mmol), 1-hydroxybenzotriazole (HOBT) (66 mg, 0.49 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-teramethyluronium

tetrafluoroborate (TBTU) (315 mg, 0.98 mmol), *N,N*-diisopropylethylamine (DIPEA) (192 µl, 2.205 mmol) in 1-methylpyrrolidine (2 ml) was added and the resultant suspension was agitated at ambient temperature for sixteen hours. The resin was filtered and was washed with 1-methylpyrrolidine (5 ml) and alternately with methanol (4 x 5 ml) and dichloromethane (4 x 5 ml). The resin was dried and a sample was analysed by IR spectroscopy (IR(resin/cm^{-1}) 1685 (amide) and 1737 (ester)).

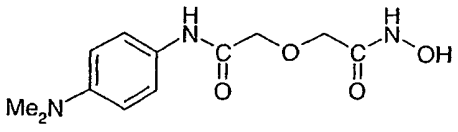
The resin (500 mg, 0.245 mmol) obtained from the second step was placed in a reaction vessel and was swollen by the addition of 1,4-dioxane (4 ml). A 50% wt solution of hydroxylamine in water (0.4 ml, 6.125 mmol) was added and the resultant suspension was agitated at ambient temperature for forty-eight hours. The resin was filtered and washed with a mixture of dioxane and water (1:1, v/v) (5 ml). The filtrates were combined and the solvent was removed under reduced pressure.

The crude product obtained was purified by preparative hplc using a 150 x 21.2 mm 5 µm Hypersil7 Elite C_{18} column eluting with a gradient of 5% ACN/95% H_2O + 0.2% TFA to 95% ACN/5% H_2O + 0.2% TFA over 10 minutes. The flow rate was 25 $mlmin^{-1}$ and the detector was set at 254 nm. The fractions that contained the desired product were concentrated under reduced pressure and the resultant residue was lyophilised from a mixture of dioxane and water to afford the desired product as a white solid (3.7 mg, 5 %), t_R 4.27 (254 nm, 3.0 $mlmin^{-1}$, 5% ACN/95% H_2O + 0.2% TFA to 95% ACN/5% H_2O + 0.2% TFA over 3.5 min then 2.5 min at 95% ACN/5% H_2O + 0.2% TFA), *m/z* [ES] 283 $[M + H]^+$.

Example 3

2-(4-Dimethylamino-phenylcarbamoyl)-methoxy)-*N*-hydroxy-acetamide

(PX089281)



ArgoGelJ-OH resin (500 mg, 0.245 mmol) was placed in a reaction vessel and was swollen by the addition of dichloromethane / pyridine (1:1, v/v) (2 ml). A solution of thiodiglycolic anhydride (162 mg. 1.225 mmol), and 4-(dimethylamino)pyridine (DMAP) (15 mg, 0.1225 mmol) in dichloromethane / pyridine (1:1, v/v) (2 ml) was added and the resultant suspension was agitated at ambient temperature for sixteen hours. The resin was filtered and was washed with 1-methylpyrrolidine (5 ml) and alternately with methanol (4 x 5 ml) and dichloromethane (4 x 5 ml). The resin was dried and a sample was analysed by IR spectroscopy (IR(resin/cm^{-1}) 1732 (ester)).

The resin (500 mg, 0.245 mmol) obtained from the first step was placed in a reaction vessel and was swollen by the addition of 1-methylpyrrolidine (2 ml). A solution of *N,N*-dimethylamino-1,4-phenylenediamine (133 mg, 0.98 mmol), 1-hydroxybenzotriazole (HOBT) (66 mg, 0.49 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-teramethyluronium tetrafluoroborate (TBTU) (315 mg, 0.98 mmol), *N,N*-diisopropylethylamine (DIPEA) (192 µl, 2.205 mmol) in 1-methylpyrrolidine (2 ml) was added and the resultant suspension was agitated at ambient temperature for sixteen hours. The resin was filtered and was washed with 1-methylpyrrolidine (5 ml) and alternately with methanol (4 x 5 ml) and dichloromethane (4 x 5 ml). The resin was dried and a sample was analysed by IR spectroscopy (IR(resin/cm^{-1}) 1684 (amide) and 1751 (ester)).

The resin (500 mg, 0.245 mmol) obtained from the second step was placed in a reaction vessel and was swollen by the addition of 1,4-dioxane (4 ml). A 50% wt solution of hydroxylamine in water (0.4 ml, 6.125 mmol) was added and the resultant suspension was agitated at ambient temperature for forty-eight hours. The resin was filtered and washed with a mixture of dioxane and water (1:1, v/v) (5 ml). The filtrates were combined and the solvent was removed under reduced pressure.

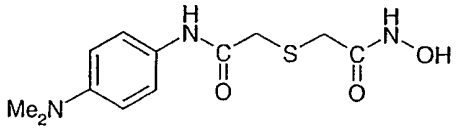
The crude product obtained was purified by preparative hplc using a 150 x 21.2 mm 5 µm Hypersil7 Elite C_{18} column eluting with a gradient of 5% ACN/95% H_2O + 0.2% TFA to 95% ACN/5% H_2O + 0.2% TFA over 10 minutes. The flow rate

was 25 mlmin^{-1} and the detector was set at 254 nm. The fractions that contained the desired product were concentrated under reduced pressure and the resultant residue was lyophilised from a mixture of dioxane and water to afford the desired product as a white solid (37.9 mg, 58 %), t_R 0.50 (254 nm, 3.0 mlmin^{-1}, 5% ACN/95% H_2O + 0.2% TFA to 95% ACN/5% H_2O + 0.2% TFA over 3.5 min then 2.5 min at 95% ACN/5% H_2O + 0.2% TFA).

Example 4

2-((4-Dimethylamino-phenylcarbamoyl)-methylsulfanyl)-*N*-hydroxy-acetamide

(**PX089278**)



ArgoGelJ-OH resin (500 mg, 0.245 mmol) was placed in a reaction vessel and was swollen by the addition of dichloromethane / pyridine (1:1, v/v) (2 ml). A solution of thiodiglycolic anhydride (162 mg, 1.225 mmol), and 4-(dimethylamino)pyridine (DMAP) (15 mg, 0.1225 mmol) in dichloromethane / pyridine (1:1, v/v) (2 ml) was added and the resultant suspension was agitated at ambient temperature for sixteen hours. The resin was filtered and was washed with 1-methylpyrrolidine (5 ml) and alternately with methanol (4 x 5 ml) and dichloromethane (4 x 5 ml). The resin was dried and a sample was analysed by IR spectroscopy (IR(resin/cm^{-1}) 1732 (ester)).

The resin (500 mg, 0.245 mmol) obtained from the first step was placed in a reaction vessel and was swollen by the addition of 1-methylpyrrolidine (2 ml). A solution of *N,N*-dimethyl-1,4-phenylenediamine (133 mg, 0.98 mmol), 1-hydroxybenzotriazole (HOBT) (66 mg, 0.49 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-teramethyluronium tetrafluoroborate (TBTU) (315 mg, 0.98 mmol), *N,N*-diisopropylethylamine (DIPEA) (192 µl, 2.205 mmol) in 1-methylpyrrolidine (2 ml) was added and the resultant suspension was agitated at ambient temperature for sixteen hours. The resin was filtered and was washed with 1-methylpyrrolidine (5 ml) and alternately with methanol (4 x 5 ml) and dichloromethane (4 x 5 ml). The

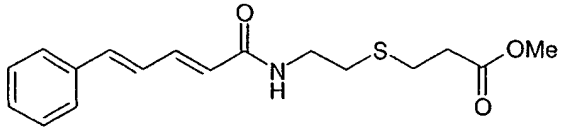
resin was dried and a sample was analysed by IR spectroscopy (IR(resin/cm^{-1}) 1678 (amide) and 1736 (ester)).

The resin (500 mg, 0.245 mmol) obtained from the second step was placed in a reaction vessel and was swollen by the addition of 1,4-dioxane (4 ml). A 50% wt solution of hydroxylamine in water (0.4 ml, 6.125 mmol) was added and the resultant suspension was agitated at ambient temperature for forty-eight hours. The resin was filtered and washed with a mixture of dioxane and water (1:1, v/v) (5 ml). The filtrates were combined and the solvent was removed under reduced pressure.

The crude product obtained was purified by preparative hplc using a 150 x 21.2 mm 5 µm Hypersil7 Elite C_{18} column eluting with a gradient of 5% ACN/95% H_2O + 0.2% TFA to 95% ACN/5% H_2O + 0.2% TFA over 10 minutes. The flow rate was 25 $mlmin^{-1}$ and the detector was set at 254 nm. The fractions that contained the desired product were concentrated under reduced pressure and the resultant residue was lyophilised from a mixture of dioxane and water to afford the desired product as a brown oil (3.3 mg, 5 %), t_R 0.44 (254 nm, 3.0 $mlmin^{-1}$, 5% ACN/95% H_2O + 0.2% TFA to 95% ACN/5% H_2O + 0.2% TFA over 3.5 min then 2.5 min at 95% ACN/5% H_2O + 0.2% TFA), *m/z* [ES] 284 $[M + H]^+$.

Example 5

3-{2-[(2E)(4E)-5-Phenylpenta-2,4-dienoylamino]ethylsulfanyl}propionic acid methyl ester (**3/28**)

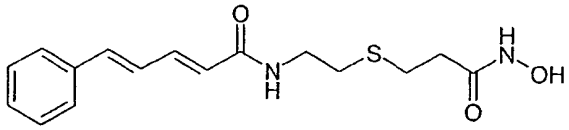


1,1'-Carbonyldiimidazole (0.36 g, 2.2 mmol) was added to a solution of 5-phenyl-penta-2*E*,4*E*-dienoic acid (**1/1**) (0.35 g, 2 mmol) in dry tetrahydrofuran (10 ml) and the obtained mixture was stirred for 1 hour at ambient temperature. To the mixture triethylamine (0.30 g 3.0 mmol) and methyl 3-(2-amino-ethylsulfanyl)-propionate hydrochloride (**2e**) (2.2 mmol) were added and the resultant suspension was stirred for 6 hours at ambient temperature. The solvent was removed under

reduced pressure, to the residue water (15 ml) was added and the precipitate was filtered off, washed with water and dried, to give the title product. Yield 67%, m.p. 58-60°C. ^{1}H NMR (90 MHz, DMSO-d_6) δ: 2.54-2.89 (6H, m, CH_2); 2.96-3.45 (2H, m, CH_2); 3.61 (3H, s, CH_3); 6.14 (1H, d, J=14.5 Hz, CH); 6.81-7.16 (2H, m, CH-CH); 7.11-7.69 (6H, m, C_6H_5, CH); 8.18 (1H, t, J=5.4 Hz, NH).

Example 6

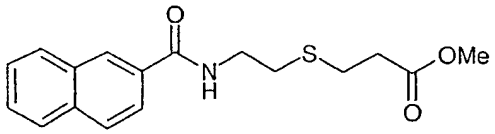
(2E)(4E)-5-Phenylpenta-2,4-dienoic acid [2-(2-hydroxycarbamoylethylsulfanyl)ethyl]amide (**PX117439**)



A solution of sodium methylate (6 mmol) in methanol (5 ml) was added to a solution of hydroxylamine hydrochloride (0.28 g, 4 mmol) in methanol (8 ml). A mixture was stirred for 10 min. and the precipitate was filtered off. 3-{2-[(2E)(4E)-5-phenylpenta-2,4-dienoylamino]ethylsulfanyl}propionic acid methyl ester (**3/28**) (1 mmol) was added to the filtrate and the mixture was heated to the complete dissolving. The resultant mixture was stirred for 4 hours at ambient temperature and the solvent was removed under reduced pressure. The product was dissolved in water (10 ml) and acidified with 3% HCl. Precipitate was filtered off and crystallized from methanol. Yield 47%, m.p. 158-160°C. ^{1}H NMR (90 MHz, DMSO-d_6) δ: 2.24 (2H, t, J=6.8 Hz, CH_2); 2.56-2.87 (4H, m, CH_2); 3.29 (2H, q, J=6.0 Hz, CH_2); 6.14 (1H, d, J=15.0 Hz, CH); 6.83-7.14 (2H, m, CH-CH); 7.14-7.66 (6H, m, C_6H_5, CH); 8.21 (1H, t, J=5.5 Hz, NH); 8.74 (1H, s, NH), 10.42 (1H, s, OH). HPLC analysis on Symmetry C_{18} column: impurities 2.6 % (column size 3.9 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 35:65; detector UV 230 nm; sample concentration 0.3 mg/ml). Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C 59.98, H 6.29, N 8.74. Found: C 59.82, H 6.23, N 8.68.

Example 7

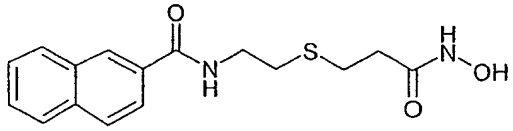
E-3-{2-[(Naphthalene-2-carbonyl)amino]ethylsulfanyl}propionic acid methyl ester (**3/29**)



Using an analogous method, the title compound was obtained from naphthalene-2-carboxylic acid (**1/29**) and methyl 3-(2-amino-ethylsulfanyl)-propionate hydrochloride (**2e**). Yield 60%, m.p. 73-75°C. ^{1}H NMR (90 MHz, DMSO-d_6) δ: 2.58-2.93 (6H, m, CH_2); 3.36-3.58 (2H, m, CH_2); 3.61 (3H, s, CH_3); 7.45-7.78 (2H, m, $C_{10}H_2$); 7.81-8.17 (4H, m, $C_{10}H_4$); 8.45 (1H, s, $C_{10}H$); 8.78 (1H, t, J=5.2 Hz, NH).

Example 8

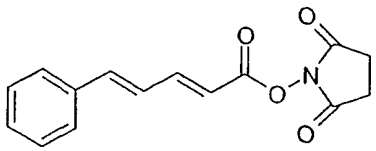
E-Naphthalene-2-carboxylic acid [2-(2-hydroxycarbamoylethylsulfanyl) ethyl]amide (**PX117440**)



Using an analogous method, the title compound was obtained from E-3-{2-[(naphthalene-2-carbonyl)amino]ethylsulfanyl} propionic acid methyl ester (**3/29**). Yield 88%, m.p. 128-130°C. ^{1}H NMR (90 MHz, DMSO-d_6) δ: 2.27 (2H, t, J=6.7 Hz, CH_2); 2.58-2.92 (4H, m, CH_2); 3.49 (2H, q, J=5.5 Hz, CH_2); 7.52-7.74 (2H, m, $C_{10}H_2$); 7.87-8.18 (4H, m, $C_{10}H_4$); 8.47 (1H, s, $C_{10}H$); 8.78 (1H, t, J=5.5 Hz, NH), 10.21 (2H, br s, OH, NH). HPLC analysis on Symmetry C_{18} column: impurities 1.0 % (column size 3.9 x 150 mm; mobile phase acetonitrile – 0.1M phosphate buffer (pH 2.5), 35:65; detector UV 230 nm; sample concentration 0.5 mg/ml). Anal. Calcd for $C_{16}H_{18}N_2O_5S$: C 60.36, H 5.70, N 8.80 Found: C 60.12, H 5.56, N 8.61.

Example 9

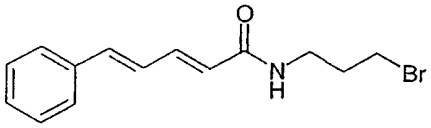
5-Phenyl-penta-2,4-dienoic acid 2,5-dioxo-pyrrolidin-1-yl ester (**10**)



To the solution of 5-phenyl-penta-2,4-dienoic acid (**1/1**) (8.00 g, 46.0 mmol) in anhydrous methylene chloride (350 ml) N-hydroxysuccinimide (5.29 g, 46.0 mmol) was added and the mixture was cooled in the ice bath. A solution of N,N'-dicyclohexylcarbodiimide (10.44 g, 50.6 mmol) in anhydrous methylene chloride (100 ml) slowly was added and the resulting mixture was stirred at ambient temperature for 4 hours. The precipitate was filtered off and washed with ethanol. The filtrate was evaporated and dried to give the title compound **10** (10.48 g, 84%). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 2.85 (4H, s); 6.14 (1H, d, J=15.0 Hz); 6.75-7.18 (2H, m); 7.29-7.63 (6H, m).

Example 10

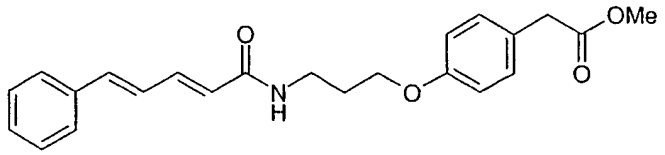
5-Phenyl-penta-2,4-dienoic acid (3-bromo-propyl)-amide (**11**)



To a suspension of 3-bromopropylamine hydrobromide (1.09 g, 5.0 mmol) in anhydrous methylene chloride triethylamine (0.61 g, 6.0 mmol) was added and the mixture was stirred at ambient temperature for 30 min. The mixture was cooled in the ice bath and a solution of 5-phenyl-penta-2,4-dienoic acid 2,5-dioxo-pyrrolidin-1-yl ester (**10**) (1.35 g, 5.0 mol) in methylene chloride (20 ml) was added. The reaction mixture was stirred at ice bath temperature for 1.5 hours and at ambient temperature for 2 hours. The solvent was removed and the residue was suspended in water. The precipitate was filtered and washed with water and hexane to give the title compound **11** (1.0 g, 68%). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.92-2.32 (2H, m); 3.31-3.67 (4H, m); 6.00 (1H, d, J=15.0 Hz); 6.07 (1H, br s); 6.78-6.96 (2H, m); 7.22-7.61 (6H, m).

Example 11

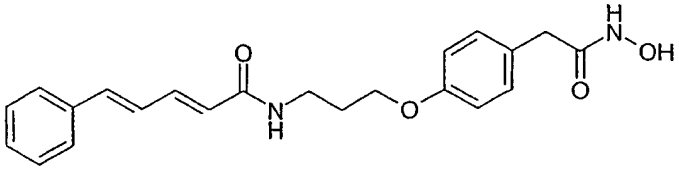
4-[3-(5-Phenyl-penta-2,4-dienoylamino)-propoxy]-phenyl}-acetic acid methyl ester (**12**)



To a suspension of NaH (60% in mineral oil, 0.18 g, 4.5 mmol) in dimethylformamide (2 ml) at ice bath temperature a solution of methyl 4-hydroxyphenylacetate (0.5 g, 3.0 mmol) in dimethylformamide (2 ml) slowly was added. The resulting mixture was stirred for 1 hour at this temperature, then a solution of 5-phenylpenta-2,4-dienoic acid (3-bromo-propyl)-amide (**11**) was added. The reaction mixture was stirred at 110°C for 2 hours, cooled down to room temperature and diluted with water (10 ml). The pH of the medium was brought to 5 with 1N HCl and the mixture was extracted with ethyl acetate. The organic layer was washed successively with 2N NaOH, water, brine, and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silicagel with methylene chloride-acetone (9:1) as eluent to give the title product **12** (0.240 g, 32%), m.p. 104-106°C. ^{1}H NMR ($CDCl_3$, HMDSO) δ: 1.81-2.21 (2H, m); 3.37-3.62 (4H, m); 3.66 (3H, s); 4.04 (2H, t); 5.94 (1H, d, J=15.0 Hz); 6.03 (1H, br s); 6.75-6.98 (4H, m); 7.09-7.58 (8H, m).

Example 12

(2E,4E)-N-(3-{4-[2-(Hydroxyamino)-2-oxoethyl]phenoxy}propyl)-5-phenyl-2,4-pentadienamide (**PX117443**)

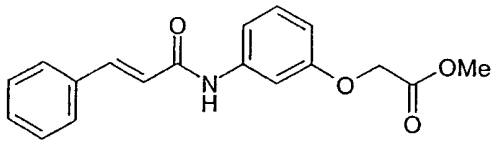


To a solution of 4-[3-(5-phenyl-penta-2,4-dienoylamino)-propoxy]-phenyl}-acetic acid methyl ester (**12**) (0.24 g, 0.632 mmol) in methanol (5 ml) and dioxane (2 ml) at ambient temperature a solution of hydroxylamine hydrochloride (0.176 g, 2.529 mmol) in methanol (3 ml) was added. The reaction mixture was cooled in the ice

bath and a solution of NaOH (0.20 g, 5.059 mmol) in water (1 ml) was added. The reaction mixture was stirred at ambient temperature for 1.5 hours and then pH of the medium was brought to 4 with 1N HCl. The mixture immediately was extracted with ethyl acetate (120 ml). The organic layer was washed successively with 5% NaOH, water, brine, and dried (Na_2SO_4). The solvent was partially removed, the precipitate was filtered and crystallized from acetonitrile-ethanol (1:1) to give the title compound (0.22 g, 91%). M.p. 198-201°C. ^{1}H NMR (DMSO-d_6, HMDSO), δ: 1.78-1.98 (2H, m, CH_2); 3.19 (2H, s, CH_2); 3.20-3.40 (2H, t, CH_2, overlapped with a signal of H_2O); 3.97 (2H, t, J=6.2 Hz, CH_2); 6.14 (1H, d, J=14.4 Hz, CH); 6.85 (2H, d, J=8,6 Hz, C_6H_2); 6.94-7.05 (2H, m, =CH-CH=); 7.09-7.42 (6H, m, C_6H_5 and –CH=); 7.50-7.61 (2H, m, C_6H_2); 8.18 (1H, t, J=5.4 Hz, NH); 8.79 (1H, s, NH); 10.59 (1H, s, OH). HPLC analysis on Symmetry C_{18} column: impurities ~3 % (column size 3.9 x 150 mm; mobile phase acetonitrile-0.1 M phosphate buffer (40:60), pH 2.5; detector UV 230 nm; sample concentration 0.1 mg/ml, flow rate 1.0 ml/min). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C 69.46, H 6.36, N 7.36. Found: C 69.31, H 6.34, N 7.28.

Example 13

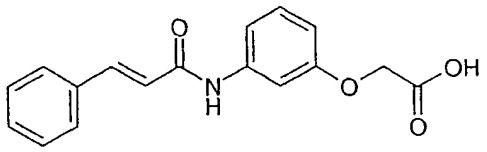
[3-(3-Phenyl-acryloylamino)-phenoxy]-acetic acid methyl ester (**8**)



A mixture of methyl bromoacetate (0.230 g, 1.93 mmol), Cs_2CO_3 (0.525 g, 1.60 mmol), and N-(3-hydroxy-phenyl)-3-phenyl-acrylamide (**1/91**) (0.370 g, 1.55 mmol) in acetonitrile (5 ml) was stirred at 45°C for 3 hours. The reaction mixture was evaporated and the residue was partitioned between ethyl acetate and 0.1N $KHSO_4$. The organic layer was washed successively with water, brine, and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed silicagel with chloroform-ethyl acetate (10:1) as eluent to give the title compound **8** (0.235 g, 48%). ^{1}H NMR ($CDCl_3$, HMDSO) δ: 3.75 (3H, s); 4.62 (2H, s); 6.53 (1H, d, J=15.6 Hz); 6.68 (1H, t, J=2.0 Hz); 7.01-7.60 (9H, m); 7.71 (1H, d, J=15.6 Hz).

Example 14

[3-(3-Phenyl-acryloylamino)-phenoxy]-acetic acid (**9**)

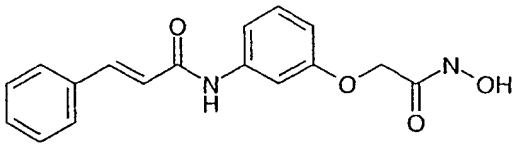


To a suspension of [3-(3-phenyl-acryloylamino)-phenoxy]-acetic acid methyl ester (**8**) (0.345 g, 1.1 mmol) in tetrahydrofuran (6 ml) a solution of NaOH (0.130 g, 3.3 mmol) in water (6 ml) was added and the resulting mixture was stirred for 3 hours at 35°C. Tetrahydrofuran was evaporated and the remaining water mixture was acidified with 2N HCl to pH 3. The precipitate was filtered off and dried to give 0.300 g (92%) of the title product **9**, which was used in the next step without an additional purification.

Example 15

(E)-N-{3-[2-(Hydroxyamino)-2-oxoethoxy]phenyl}-3-phenyl-2-propenamide

(**PX117708**)



To a solution of [3-(3-phenyl-acryloylamino)-phenoxy]-acetic acid (**9**) (0.297 g, 1.0 mmol) in tetrahydrofuran (3 ml) at 0÷5°C temperature (ice bath) triethylamine (0.18 ml, 1.3 mmol) followed by iso-butyl chloroformate (0.15 ml, 1.15 mmol) were added. The reaction mixture was stirred for 20 min. In another vessel, a mixture of hydroxylamine hydrochloride (0.122 g, 1.7 mmol) and sodium methoxide (0.095 mg, 1.75 mmol) was prepared. The both mixtures were combined and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was extracted with ethyl acetate (20 ml) and the organic layer was washed successively with 1N KH_2PO_4, water, brine, and dried (Na_2SO_4). The solvent was partially removed until the formation of a precipitate started. The mixture was allowed to stand at room temperature for 6 hours. The precipitate was filtered and washed with diethyl ether to give the title compound (0.090 g, 30%). M.p. 163°C (dec.). ^{1}H NMR (DMSO-d_6, HMDSO), δ: 4.45 (s, 2H); 6.60-6.73 (m, 1H); 6.83 (d,

1H, J=15.6 Hz); 7.18-7.30 (m, 2H); 7.36-7.51 (m, 4H); 7.53-7.68 (m, 3H); 8.98 (s, 1H); 10.23 (s, 1H); 10.87 (s, 1H). HPLC analysis on Zorbax SB-C18 column: impurities ~1 % (column size 4.6 x 150 mm; mobile phase acetonitrile – 0.1% H_3PO_4, gradient from 50:50 to 100:0; detector UV 270 nm; sample concentration 0.7 mg/ml, flow rate 1.0 ml/min). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C 65.38, H 5.16, N 8.97. Found: C 65.09, H 5.14, N 8.73.

Biological Activity

Candidate compounds were assessed for their ability to inhibit deacetylase activity (biochemical assays) and to inhibit cell proliferation (cell-based antiproliferation assays), as described below.

Primary Assay: Deacetylase Activity

Briefly, this assay relies on the release of radioactive acetate from a radioactively labelled histone fragment by the action of HDAC enzyme. Test compounds, which inhibit HDAC, reduce the yield of radioactive acetate. Signal (e.g., scintillation counts) measured in the presence and absence of a test compound provide an indication of that compound's ability to inhibit HDAC activity. Decreased activity indicates increased inhibition by the test compound.

The histone fragment was an N-terminal sequence from histone H4, and it was labelled with radioactively labelled acetyl groups using tritiated acetylcoenzyme A (coA) in conjunction with an enzyme which is the histone acetyltransferase domain of the transcriptional coactivator p300. 0.33 mg of peptide H4 (the N-terminal 20 amino acids of histone H4, synthesized using conventional methods) were incubated with His6-tagged p300 histone acetyltransferase domain (amino acids 1195-1673, expressed in *E. coli* strain BLR(DE3)pLysS (Novagen, Cat. No. 69451-3) and 3H-acetyl coA (10 µL of 3.95 Ci/mmol; from Amersham) in a total volume of 300 µL of HAT buffer (50 mM TrisCl pH 8, 5% glycerol, 50 mM KCl, 0.1 mM ethylenediaminetetraacetic acid (EDTA), 1 mM dithiothreitol (DTT) and 1 mM 4-(2-aminoethyl)-benzenesulfonylfluoride (AEBSF)). The mixture was

incubated at 30°C for 45 min after which the His-p300 was removed using nickel-trinitriloacetic acid agarose (Qiagen, Cat No. 30210). The acetylated peptide was then separated from free acetyl coA by size exclusion chromatography on Sephadex G-15 (Sigma G-15-120), using distilled H_2O as the mobile phase.

After purification of the radiolabelled histone fragment, it was incubated with a source of HDAC (e.g., an extract of HeLa cells (a rich source of HDAC), recombinantly produced HDAC1 or HDAC2) and any released acetate was extracted into an organic phase and quantitatively determined using scintillation counting. By including a test compound with the source of HDAC, that compound's ability to inhibit the HDAC was determined.

HeLa Cell Extract

The HeLa cell extract was made from HeLa cells (ATCC Ref. No. CCL-2) by freeze-thawing three times in 60 mM TrisCl pH 8.0, 450 mM NaCl, 30% glycerol. Two cell volumes of extraction buffer were used, and particulate material was centrifuged out (20800 g, 4°C, 10 min). The supernatant extract having deacetylase activity was aliquotted and frozen for storage.

Recombinantly Produced HDAC1 and HDAC2

Recombinant plasmids were prepared as follows.

Full length human HDAC1 was cloned by PCR using a λgt11 Jurkat cDNA library (Clontech-HL5012b). The amplified fragment was inserted into the EcoRI-SalI sites of pFlag-CTC vector (Sigma-E5394), in frame with the Flag tag. A second PCR was carried out in order to amplify a fragment containing the HDAC1 sequence fused to the Flag tag. The resulting fragment was subcloned into the EcoRI-Sac1 sites of the baculovirus transfer vector pAcHTL-C (Pharmingen-21466P).

Full length human HDAC2 was subcloned into pAcHLT-A baculovirus transfer vector (Pharmingen-21464P) by PCR amplification of the EcoRI-Sac1 fragment from a HDAC2-pFlag-CTC construct.

Recombinant protein expression and purification was performed as follows.

HDAC1 and HDAC2 recombinant baculoviruses were constructed using BaculoGold Transfection Kit (Pharmingen-554740). Transfer vectors were co-transfected into SF9 insect cells (Pharmingen-21300C). Amplification of recombinant viruses was performed according to the Pharmingen Instruction Manual. SF9 cells were maintained in serum-free SF900 medium (Gibco 10902-096).

For protein production, $2x10^7$ cells were infected with the appropriate recombinant virus for 3 days. Cells were then harvested and spun at 3,000 rpm for 5 minutes. They were then washed twice in PBS and resuspended in 2 pellet volumes of lysis buffer (25 mM HEPES pH 7.9, 0.1 mM EDTA, 400 mM KCl, 10% glycerol, 0.1% NP-40, 1 mM AEBSF). Resuspended cells were frozen on dry ice and thawed at 37°C 3 times and centrifuged for 10 minutes at 14,000 rpm. The supernatant was collected and incubated with 300 µl of 50% Ni-NTA agarose bead slurry (Qiagen-30210). Incubation was carried out at 4°C for 1 hour on a rotating wheel. The slurry was then centrifuged at 500 g for 5 minutes. Beads were washed twice in 1 ml of wash buffer (25 mM HEPES pH7.9, 0.1 mM EDTA, 150 mM KCl, 10% glycerol, 0.1% NP-40, 1 mM AEBSF). Protein was eluted 3 times in 300 µl elution buffer (25 mM HEPES pH 7.9, 0.1 mM EDTA, 250 mM KCl, 10% glycerol, 0.1% NP-40, 1 mM AEBSF) containing increasing concentrations of imidazole: 0.2 M, 0.5 M and 1 M. Each elution was performed for 5 minutes at room temperature. Eluted protein was kept in 50% glycerol at -70°C.

Assay Method

A source of HDAC (e.g., 2 µL of crude HeLa extract, 5 µL of HDAC1 or HDAC2; in elution buffer, as above) was incubated with 3 µL of radioactively labelled peptide

along with appropriate dilutions of candidate compounds (1.5 µL) in a total volume of 150 µL of buffer (20 mM Tris pH 7.4, 10% glycerol). The reaction was carried out at 37°C for one hour, after which the reaction was stopped by adding 20 µL of 1 M HCl / 0.4 M sodium acetate. Then, 750 µL of ethyl acetate was added, the samples vortexed and, after centrifugation (14000 rpm, 5 min), 600 µL from the upper phase were transferred to a vial containing 3 mL of scintillation liquid (UltimaGold, Packard, Cat. No. 6013329). Radioactivity was measured using a Tri-Carb 2100TR Liquid Scintillation Analyzer (Packard).

Percent activity (% activity) for each test compound was calculated as:

$$\% \text{ activity} = \{ (S^C - B) / (S° - B) \} \times 100$$

wherein S^C denotes signal measured in the presence of enzyme and the compound being tested, S° denotes signal measured in the presence of enzyme but in the absence of the compound being tested, and B denotes the background signal measured in the absence of both enzyme and compound being tested. The IC50 corresponds to the concentration which achieves 50% activity.

IC50 data for several compounds of the present invention, as determined using this assay, are also shown in Table 1, below.

Measurement of cell viability in the presence of increasing concentration of test compound at different time points is used to assess both cytotoxicity and the effect of the compound on cell proliferation.

Secondary Assay: Cell Proliferation

Compounds with HDAC inhibition activity, as determined using the primary assay, were subsequently evaluated using secondary cell-based assays. The following cell lines were used:

HeLa - Human cervical adenocarcinoma cell line (ATCC ref. No. CCL-2).

K11 – HPV E7 transformed human keratinocyte line provided by Pidder Jansen-Duerr, Institut für Biomedizinische Alternsforschung, Innsbruck, Austria.

NHEK-Ad – Primary human adult keratinocyte line (Cambrex Corp., East Rutherford, NJ, USA).

JURKAT – Human T-cell line (ATCC no. TIB-152).

Assay Method

Cells were cultured, exposed to candidate compounds, and incubated for a time, and the number of viable cells was then assessed using the Cell Proliferation Reagent WST-1 from Boehringer Mannheim (Cat. No. 1 644 807), described below.

Cells were plated in 96-well plates at 3-10x10^3 cells/well in 100 µL of culture medium. The following day, different concentrations of candidate compounds were added and the cells incubated at 37°C for 48 h. Subsequently, 10 µL/well of WST-1 reagent was added and the cells reincubated for 1 hour. After the incubation time, absorbance was measured.

WST-1 is a tetrazolium salt which is cleaved to formazan dye by cellular enzymes. An expansion in the number of viable cells results in an increase in the overall activity of mitochondrial dehydrogenases in the sample. This augmentation in the enzyme activity leads to an increase in the amount of formazan dye formed, which directly correlates to the number of metabolically active cells in the culture. The formazan dye produced is quantified by a scanning multiwell spectrophotometer by measuring the absorbance of the dye solution at 450 nm wavelength (reference wavelength 690 nm).

Percent activity (% activity) in reducing the number of viable cells was calculated for each test compound as:

$$\% \text{ activity} = \{ (S^C - B) / (S^\circ - B) \} \times 100$$

wherein S^C denotes signal measured in the presence of the compound being tested, S° denotes signal measured in the absence of the compound being tested, and B denotes the background signal measured in blank wells containing medium only. The IC50 corresponds to the concentration which achieves 50% activity. IC50 values were calculated using the software package Prism 3.0 (GraphPad Software Inc., San Diego, CA) , setting top value at 100 and bottom value at 0.

IC50 data for several compounds of the present invention, as determined using this assay, are also shown in Table 2, below.

Measurement of cell viability in the presence of increasing concentration of test compound at different time points is used to assess both cytotoxicity and the effect of the compound on cell proliferation.

Biological Data

IC50 (or percent activity) data for several compounds of the present invention, as determined using the assays described above are summarised in Table 1 and Table 2, below.

Table 1
Biochemical Assay Data

Compound		HDAC Inhibition (IC50 unless otherwise specified)		
No.	Ref.	HeLa	HDAC1	HDAC2
TSA	-	5 nM	15 nM	17 nM
1	PX083805	16%@1.0μM	-	-
2	PX089278	26%@500 nM	-	-
3	PX089279	55 μM	-	-
4	PX089281	0% @1 μM	-	-
5	PX117439	74%@500 nM	-	-
6	PX117440	43%@500 nM	-	-
7	PX117443	7%@500 nM	-	-
8	PX117708	750	-	-

Table 2
Cell-Based Antiproliferation Assay Data

Compound		Cell Proliferation Inhibition WST-1 (IC50 unless otherwise specified)			
No.	Ref.	HeLa	K11	NHEK-AD	Jurkat
	TSA	350 nM	0.38 μM	0.2 μM	42 nM
	Oxamflatin	-	4.82 μM	3.53 μM	170 nM
	MS-275	-	9.16 μM	3.1 μM	365 nM
	SAHA	-	6.82 μM	5.37μM	750 nM
1	PX083805	-	-	-	-
2	PX089278	-	-	-	-
3	PX089279	213 μM	-	-	-
4	PX089281	-	-	-	-
5	PX117439	87 μM	-	-	-
6	PX117440	-	-	-	-
7	PX117443	-	-	-	-
8	PX117708	25 μM	1.05 μM	-	12.7 μM

REFERENCES

A number of patents and publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided herein. Each of these references is incorporated herein by reference in its entirety into the present disclosure.

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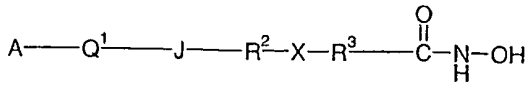
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CLAIMS

1. A compound of the formula:



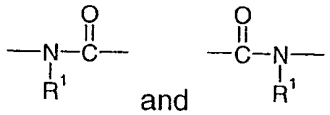
(1)

wherein:

A is an aryl group;

Q^1 is a covalent bond or an aryl leader group;

J is an amide linkage selected from:



and

R^1 is an amido substituent;

X is an ether heteroatom, and is -O- or -S-; and,

R^2 and R^3 are each independently an ether group;

and wherein:

A, is a C_{5-20}aryl group, and is optionally substituted;

the aryl leader group, if present, is a C_{1-7}alkylene group and is optionally substituted;

the amido substituent, R^1, is hydrogen, C_{1-7}alkyl, C_{3-20}heterocyclyl, or C_{5-20}aryl;

each of the ether groups, R^2 and R^3, is independently C_{1-7}alkylene; C_{5-20}arylene; C_{5-20}arylene-C_{1-7}alkylene; or C_{1-7}alkylene-C_{5-20}arylene; and is optionally substituted;

and pharmaceutically acceptable salts, solvates, amides, esters, ethers, chemically protected forms, and prodrugs thereof.

2. A compound according to claim 1, wherein J is -NR^1CO- and X is -O-.

3. A compound according to claim 1, wherein J is -NR^1CO- and X is -S-.

4. A compound according to claim 1, wherein Q^1 is an aryl leader group, J is $-NR^1CO-$ and X is -O-.

5. A compound according to claim 1, wherein Q^1 is an aryl leader group, J is $-NR^1CO-$ and X is -S-.

6. A compound according to claim 1, wherein Q^1 is a covalent bond, J is $-NR^1CO-$ and X is -O-.

7. A compound according to claim 1, wherein Q^1 is a covalent bond, J is $-NR^1CO-$ and X is -S-.

8. A compound according to claim 1, wherein J is $-CONR^1-$ and X is -O-.

9. A compound according to claim 1, wherein J is $-CONR^1-$ and X is -S-

10. A compound according to claim 1, wherein Q^1 is a covalent bond, J is $-CONR^1-$ and X is -O-.

11. A compound according to claim 1, wherein Q^1 is a covalent bond, J is $-CONR^1-$ and X is -S-.

12. A compound according to claim 1, wherein Q^1 is an aryl leader group, J is $-CONR^1-$ and X is -O-.

13. A compound according to claim 1, wherein Q^1 is an aryl leader group, J is $-CONR^1-$ and X is -S-.

14. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a saturated C_{1-7}alkylene group.

15. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a partially unsaturated C_{1-7}alkylene group.

16. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is an aliphatic C_{1-7}alkylene group.

17. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a linear C_{1-7}alkylene group.

18. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a branched C_{1-7}alkylene group.

19. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is an alicyclic C_{1-7}alkylene group.

20. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a saturated aliphatic C_{1-7}alkylene group.

21. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a saturated linear C_{1-7}alkylene group.

22. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a saturated branched C_{1-7}alkylene group.

23. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a saturated alicyclic C_{1-7}alkylene group.

24. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a partially unsaturated aliphatic C_{1-7}alkylene group.

25. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a partially unsaturated linear C_{1-7}alkylene group.

26. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a partially unsaturated branched C_{1-7}alkylene group.

27. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is a partially unsaturated alicyclic C_{1-7}alkylene group.

28. A compound according to any one of claims 1 to 13, wherein the aryl leader group, Q^1, is selected from: $-CH_2-$, -CH=CH-, and -CH=CH-CH=CH-.

29. A compound according to any one of claims 1 to 28, wherein the aryl leader group, Q^1, is optionally substituted with one or more groups selected from: halo, hydroxy, ether, C_{5-20}aryl, acyl, amido, and oxo.

30. A compound according to any one of claims 1 to 28, wherein the aryl leader group, Q^1, is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -OPr, -Ph, and =O.

31. A compound according to any one of claims 1 to 28, wherein the aryl leader group, Q^1, is substituted.

32. A compound according to any one of claims 1 to 28, wherein the aryl leader group, Q^1, is unsubstituted.

33. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a saturated C_{1-7}alkylene group.

34. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a partially unsaturated C_{1-7}alkylene group.

35. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently an aliphatic C_{1-7}alkylene group.

36. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a linear C_{1-7}alkylene group.

37. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a branched C_{1-7}alkylene group.

38. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently an alicyclic C_{1-7}alkylene group.

39. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a saturated aliphatic C_{1-7}alkylene group.

40. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a saturated linear C_{1-7}alkylene group.

41. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a saturated branched C_{1-7}alkylene group.

42. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a saturated alicyclic C_{1-7}alkylene group.

43. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a partially unsaturated aliphatic C_{1-7}alkylene group.

44. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a partially unsaturated linear C_{1-7}alkylene group.

45. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a partially unsaturated branched C_{1-7}alkylene group.

46. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently a partially unsaturated alicyclic C_{1-7}alkylene group.

47. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently $-(CH_2)_n-$, wherein n is an integer from 1 to 5.

48. A compound according to any one of claims 1 to 32, wherein the group R^2-X-R^3 is independently selected from the following:

$-CH_2-O-CH_2-$ and $-CH_2-S-CH_2-$;
$-CH_2-O-CH_2CH_2-$ and $-CH_2-S-CH_2CH_2-$;
$-CH_2CH_2-O-CH_2-$ and $-CH_2CH_2-S-CH_2-$;
$-CH_2-O-CH_2CH_2CH_2-$ and $-CH_2-S-CH_2CH_2CH_2-$;
$-CH_2CH_2-O-CH_2CH_2-$ and $-CH_2CH_2-S-CH_2CH_2-$;
$-CH_2CH_2CH_2-O-CH_2-$ and $-CH_2CH_2CH_2-S-CH_2-$;
$-CH_2-O-CH_2CH_2CH_2CH_2-$ and $-CH_2-S-CH_2CH_2CH_2CH_2-$;
$-CH_2CH_2-O-CH_2CH_2CH_2-$ and $-CH_2CH_2-S-CH_2CH_2CH_2-$;
$-CH_2CH_2CH_2-O-CH_2CH_2-$ and $-CH_2CH_2CH_2-S-CH_2CH_2-$;
$-CH_2CH_2CH_2CH_2-O-CH_2-$ and $-CH_2CH_2CH_2CH_2-S-CH_2-$;
$-CH_2CH_2CH_2CH_2CH_2-O-CH_2-$ and $-CH_2CH_2CH_2CH_2CH_2-S-CH_2-$;

49. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently C_{5-20}arylene, and is optionally substituted.

50. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently C_{5-6}arylene.

51. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is phenylene.

52. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently C_{5-20}arylene-C_{1-7}alkylene or C_{1-7}alkylene-C_{5-20}arylene, and is optionally substituted.

53. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently C_{5-6}arylene-C_{1-7}alkylene or C_{1-7}alkylene-C_{5-6}arylene, and is optionally substituted.

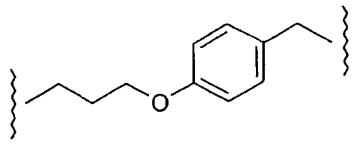
54. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently C_{1-7}alkylene-phenylene.

55. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently methylene-phenylene, ethylene-phenylene, propylene-phenylene, and ethenylene-phenylene.

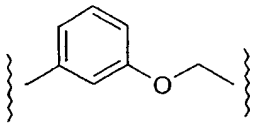
56. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently phenylene-C_{1-7}alkylene.

57. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is independently phenylene-methylene, phenylene-ethylene, phenylene-propylene, or phenylene-ethenylene.

58. A compound according to any one of claims 1 to 32, wherein the group -R^2-X-R^3- is:



59. A compound according to any one of claims 1 to 32, wherein the group -R^2-X-R^3- is:



60. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is substituted.

61. A compound according to any one of claims 1 to 32, wherein each of the ether groups, R^2 and R^3, is unsubstituted.

62. A compound according to any one of claims 1 to 61, wherein A is C_{5-20}heteroaryl or C_{5-20}carboaryl, and is optionally substituted.

63. A compound according to any one of claims 1 to 61, wherein A is a C_{5-20}aryl group derived from one of the following: benzene, pyridine, furan, indole, pyrrole, imidazole, naphthalene, quinoline, benzimidazole, benzothiofuran, fluorene, acridine, and carbazole.

64. A compound according to any one of claims 1 to 61, wherein A is an optionally substituted phenyl group.

65. A compound according to any one of claims 1 to 61, wherein A is a phenyl group optionally substituted with one or more of the following groups: fluoro, chloro, bromo, iodo, methyl, ethyl, isopropyl, t-butyl, cyano, trifluoromethyl, hydroxy, methoxy, ethoxy, isopropoxy, trifluoromethoxy,

phenoxy, methylthio, trifluoromethylthio, hydroxymethyl, amino, dimethylamino, diethylamino, morpholino, amido, acetamido, acetyl, nitro, sulfonamido, and phenyl.

66. A compound according to any one of claims 1 to 65, wherein the amido substituent, R^1, is hydrogen, C_{1-7}alkyl, or C_{5-20}aryl.

67. A compound according to any one of claims 1 to 65, wherein the amido substituent, R^1, is hydrogen or C_{1-7}alkyl.

68. A compound according to any one of claims 1 to 65, wherein the amido substituent, R^1, is -H, -Me, or -Et.

69. A compound according to any one of claims 1 to 65, wherein the amido substituent, R^1, is -H.

70. Compound PX083805.

71. Compound PX089278.

72. Compound PX089279.

73. Compound PX089281.

74. Compound PX117439.

75. Compound PX117440.

76. Compound PX117443.

77. Compound PX117708.

78. A composition comprising a compound according to any one of claims 1 to 77 and a pharmaceutically acceptable carrier or diluent.

79. A compound according to any one of claims 1 to 77 for use in a method of treatment of the human or animal body.

80. A compound according to any one of claims 1 to 77 for use in a method of treatment of a condition mediated by HDAC of the human or animal body.

81. A compound according to any one of claims 1 to 77 for use in a method of treatment of a proliferative condition of the human or animal body.

82. A compound according to any one of claims 1 to 77 for use in a method of treatment of cancer of the human or animal body.

83. A compound according to any one of claims 1 to 77 for use in a method of treatment of psoriasis of the human or animal body.

84. Use of a compound according to any one of claims 1 to 77 for the manufacture of a medicament for use in the treatment of a condition mediated by HDAC.

85. Use of a compound according to any one of claims 1 to 77 for the manufacture of a medicament for use in the treatment of a proliferative condition.

86. Use of a compound according to any one of claims 1 to 77 for the manufacture of a medicament for use in the treatment of cancer.

87. Use of a compound according to any one of claims 1 to 77 for the manufacture of a medicament for use in the treatment of psoriasis.

88. A method inhibiting HDAC in a cell comprising said cell with an effective amount of a compound according to any one of claims 1 to 77.

89. A method for the treatment of a condition mediated by HDAC comprising administering to a subject suffering from a condition mediated by HDAC a therapeutically-effective amount of a compound according to any one of claims 1 to 77.

90. A method for the treatment of a proliferative condition comprising administering to a subject suffering from a proliferative condition a therapeutically-effective amount of a compound according to any one of claims 1 to 77.

91. A method for the treatment of cancer comprising administering to a subject suffering from cancer a therapeutically-effective amount of a compound according to any one of claims 1 to 77.

92. A method for the treatment of psoriasis comprising administering to a subject suffering from psoriasis a therapeutically-effective amount of a compound according to any one of claims 1 to 77.

INTERNATIONAL SEARCH REPORT

In ›nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C323/60 C07C259/06 A61P35/00 A61P17/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MORI, TOYOKI ET AL: "Preparation of benzothiazole derivatives as protein kinase C inhibitors" retrieved from STN Database accession no. 130:352268 XP002185425 see RN 224583-79-3 abstract & JP 11 130761 A (OHTSUKA PHARMACEUTICAL CO., LTD., JAPAN) 18 May 1999 (1999-05-18) --- -/--	1,2,6, 62, 66-69, 78,79

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 December 2001	11/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bedel, C

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In ɔnal Application No
PCT/GB 01/04327

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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PCT/GB 01/04327

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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PCT/GB 01/04327

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